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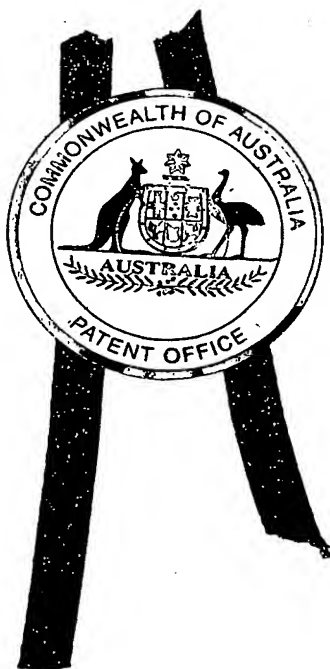
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I, JONNE YABSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002951247 for a patent by ALCHEMIA PTY LTD as filed on 06 September 2002.



WITNESS my hand this
Twelfth day of September 2003

JONNE YABSLEY
TEAM LEADER EXAMINATION
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Compounds that Interact with Kinases

FIELD OF THE INVENTION

5 The invention is directed to classes of biologically active compounds that interact in a pharmaceutically significant manner with protein kinases, and particularly to provide compounds suitable for the treatment of disorders mediated by protein kinase activity. The invention is also directed to treatment of the above mentioned disorders. The invention is also directed to the preparation of novel compounds per se.

10

BACKGROUND OF THE INVENTION

The drug discovery landscape has been transformed by the genomics revolution. Advances in the understanding of biomolecular pathways and the roles they play in disease is generating vast numbers of targets for therapeutic intervention. Protein kinases represent the second most important collection of therapeutic targets after GPCRs.

15 Kinases are key components in almost all signal transduction pathways, modulating extracellular and intracellular signalling processes that mediate events such as cell growth and differentiation, metabolism and apoptosis. Kinases do this by catalyzing the transfer of a phosphate group from ATP to protein substrates. The pivotal role of kinases is emphasized by the fact that kinases represent the third most populous domain in the proteome.

25 Kinases have been implicated in many diseases. Twenty percent of oncogenes code for tyrosine kinases. Kinases play pivotal roles in many leukemias, tumors and other proliferative disorders. Other states involving kinases include inflammatory disorders such as psoriasis, cardiovascular diseases such as restenosis, viral induced diseases such as Kaposi's sarcoma, circulatory diseases such as atherosclerosis and fibroproliferative diseases. Specific kinases are often implicated in particular disease states and therefore present themselves as potential targets for therapeutic intervention.

30

The kinase family includes serine/threonine kinases and tyrosine kinases, with the amino acid referring to the particular residue on a protein substrate that is phosphorylated. The tyrosine kinases can be further divided into receptor tyrosine kinases and non-receptor tyrosine kinases.

5 There is a continuing demand for new therapeutics, especially as our understanding of biological processes expands from the genomics revolution. Kinases are particularly suitable targets for therapeutic intervention, due to their roles in cancers, leukemia, proliferative disorders and the propagation of viral infections such as HIV and inflammation.

10 Considering the rate of generation and nature of the targets currently being deconvoluted by biologists, there is a need for the development of drug candidates, designed in a rational manner to purposely interact with selected targets, such as the kinases.

15 From a drug discovery perspective, carbohydrate pyranose and furanose rings and their derivatives are well suited as templates. Each sugar represents a three-dimensional scaffold to which a variety of substituents can be attached, usually *via* a scaffold hydroxyl group, although occasionally a scaffold carboxyl or amino group may be present for substitution. By varying the substituents, their relative position on the sugar scaffold, and the type of
20 sugar to which the substituents are coupled, numerous highly diverse structures are obtainable. An important feature to note with carbohydrates, is that molecular diversity is achieved not only in the type of substituents, but also in the three dimensional presentation. The different stereoisomers of carbohydrates that occur naturally, offer the inherent structural advantage of
25 providing alternative presentation of substituents. We have developed a system that allows the chemical synthesis of highly structurally and functionally diverse derivatised carbohydrate and tetrahydropyran structures, of both natural and unnatural origin. The diversity accessible is particularly augmented by the juxtaposition of both structural and functional aspects of the
30 molecules.

 Using the axioms of this drug discovery methodology, we synthesised several novel classes of chemotypes in an effort to develop drug candidates against kinase targets.

We selected examples from the three different kinase classes; serine/threonine kinase, tyrosine receptor kinase and tyrosine non-receptor kinase to test these molecules. These novel classes of chemotypes have provided potent and selective inhibitors against each selected kinase target.

5

SUMMARY OF THE INVENTION

It is a general object of the invention to provide compounds suitable for the treatment of disorders mediated by protein kinase activity and in the treatment of the above mentioned disorders.

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It is a further object of the invention to provide a pharmaceutical formulation comprising at least one compound as described herein or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

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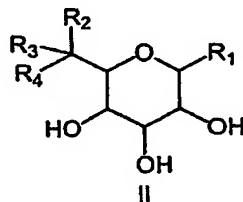
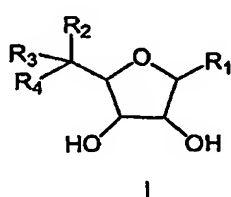
It is a further object of the invention to provide a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein kinase activity which method comprises administering to the human or animal subject an effective amount of a compound as described herein or a pharmaceutically acceptable salt thereof.

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It is a further object of the invention to prepare novel compounds per se

In one aspect the invention provides for compounds that may interact with protein kinases in a biologically significant manner of general formula I or II,

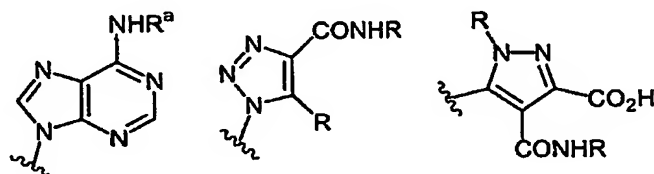
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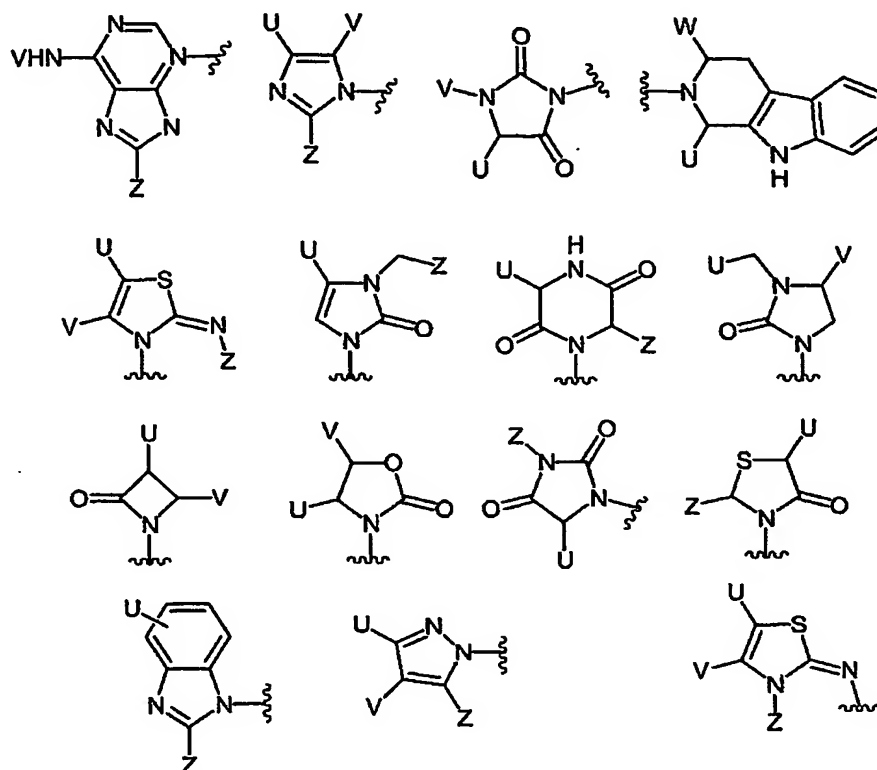
Wherein the rings may be of any configuration and the ring hydroxyl groups may be optionally substituted,

R_1 includes but is not limited to a mono or bicyclic, aryl or alkyl, mixed alkyl aryl, hetero or homo substituted or unsubstituted ring system; a nucleotide

- 5 mimetic, non-exhaustive examples are provided by the following heterocyclic structures,

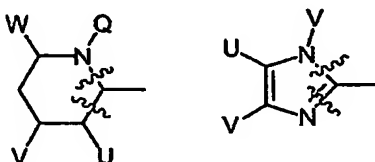


- 10 wherein R is defined as below and R^a is H or $-(CO)-R$, alternatively R_1 may be $X-R$, where X is N, O or S, and the group R includes but is not limited to H, or alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, and can be branched or linear. Typical substituents include but are not limited to
- 15 OH, NO, NO₂, NH₂, N₃, halogen, CF₃, CHF₂, CH₂F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramidate, hydrazide, hydroxamate,
- 20 hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted, R_2 and R_3 are either; both hydrogen, or are taken together to form a carbonyl function,
- R_4 includes but is not limited to $-N(T^1)T^2$ wherein T^1 and T^2 may be
- 25 independently selected from R as defined for general formula I and II, or from R^a as defined for general formula I and II, T^1 and T^2 may also be taken together to form a heterocycle, examples of which may be selected from the following non limiting selection of structures;



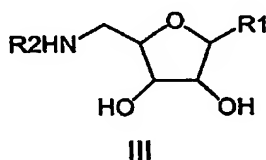
- U, V, Z are independently selected from H, or alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, and can be branched or linear. Typical substituents include but are not limited to OH, NO, NO₂, NH₂, N₃, halogen, CF₃, CHF₂, CH₂F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramidate, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted, additionally U and V may combine together to form a cycle,
- Q can be selected from the definitions of R or R^a,
- W is defined as H or -(CO)-XR,

Alternatively R_4 may be a peptide or peptide mimetic, phosphate mimetic, or R_2 and R_3 may combine with R_4 to form a cycle, non-limiting examples of which are provided by the following structure,



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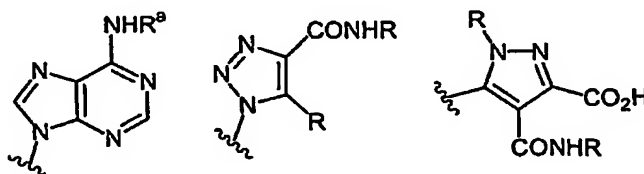
In one embodiment the invention provides compounds that may interact with protein kinases in a biologically significant manner of general formula III,



10

Wherein the ring may be of any configuration and the ring hydroxyl groups may be optionally substituted,

15 R_1 includes but is not limited to a mono or bicyclic, aryl or alkyl, mixed alkyl aryl, hetero or homo substituted or unsubstituted ring system, or a nucleotide mimetic, non-exhaustive examples are provided by the following heterocyclic structures,



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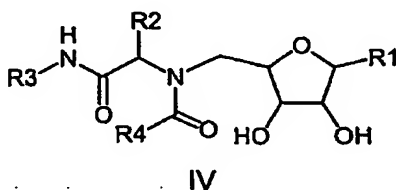
where R is defined as below and R^a is H or $-(CO)-R$,

alternatively R_1 may be $X-R$, where X is N, O or S, and group R includes but is not limited to H, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, and can be
 25 branched or linear. Typical substituents include but are not limited to OH, NO,

NO₂, NH₂, N₃, halogen, CF₃, CHF₂, CH₂F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramidate, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted, R2 is a naturally or non-naturally occurring peptide arm constituted from 1-5 amino acid monomers.

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In a second embodiment, the invention provides compounds that may interact with protein kinases in a biologically significant manner of general formula IV,



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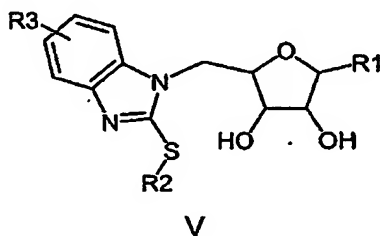
Wherein R1 is defined as for general formula III,

R2 and R4 are independantly selected from R as defined in general formula I,

R3 is a naturally or non-naturally occurring peptide arm constituted from 1-4

20 amino acid monomers.

In a third embodiment, the invention provides compounds that may interact with protein kinases in a biologically significant manner of general formula V,



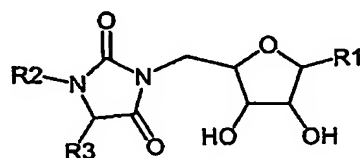
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Wherein R1 is defined as for general formula III,

R2 and R3 are independently selected from R as defined in general formula I.

In a fourth embodiment, the invention provides compounds that may interact with protein kinases in a biologically significant manner of general formula VI,

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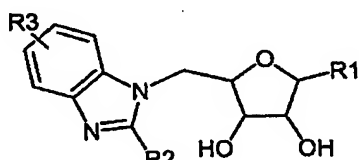


VI

Wherein R1 is defined as for general formula III, and,

10 R2 and R3 are independently selected from R as defined in general formula I.

In a fifth embodiment, the invention provides compounds that may interact with protein kinases in a biologically significant manner of general formula VII,



VII

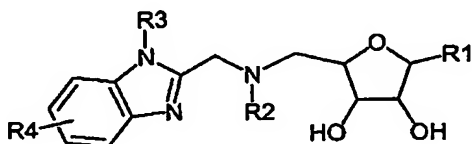
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Wherein R1 is defined as for general formula III, and,

20 R2 and R3 are independently selected from R as defined in general formula I.

20

In a sixth embodiment, the invention provides compounds that may interact with protein kinases in a biologically significant manner of general formula VIII



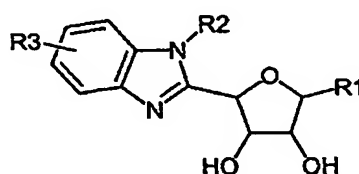
VIII

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Wherein R1 is defined as for general formula III,
 R2 can be selected from R as defined in general formula I, or from R^a as
 defined in general formula I, and,
 R3 and R4 are independently selected from R as defined in general formula I.

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In a seventh embodiment, the invention provides compounds that may
 interact with protein kinases in a biologically significant manner of general
 formula IX,



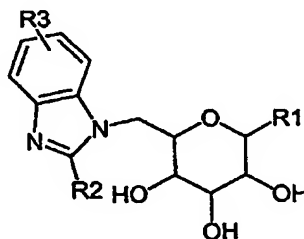
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IX

Wherein R1 is defined as for general formula III, and,
 R2 and R3 are independently selected from R as defined in general formula I..

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In an eight embodiment, the invention provides compounds that may interact
 with protein kinases in a biologically significant manner of general formula X,



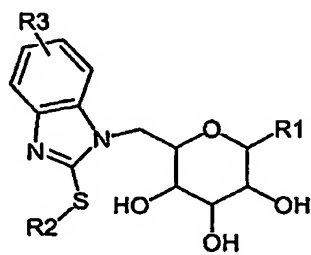
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X

Wherein R1 is defined as for general formula III, and,
 R2 and R3 selected from R as defined in general formula I.

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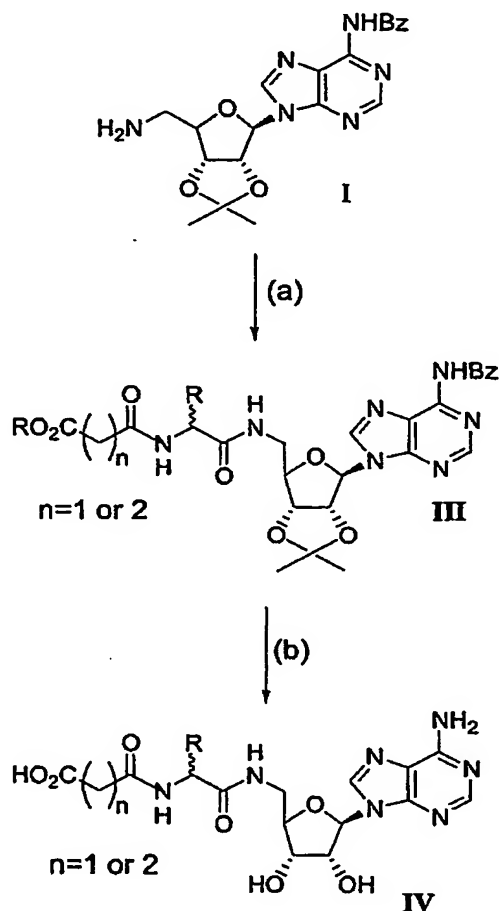
In a ninth embodiment, the invention provides compounds that may interact
 with protein kinases in a biologically significant manner of general formula XI,



XI

- 5 Wherein R1 is defined as for general formula III, and,
 R2 and R3 are independently selected from general formula I.

Example 1: General Scheme for the Solution Phase Synthesis of an Adenosine Based Libraries



5

Conditions: (a) R-CO₂H (**IIa-IIr**), HBTU, DIPEA, DMF, (b) (i) KOH, MeOH/H₂O (ii) 90/10 - TFA/H₂O. *NB. A different deprotection strategy is employed to afford the benzamido compounds.*

Step (I)

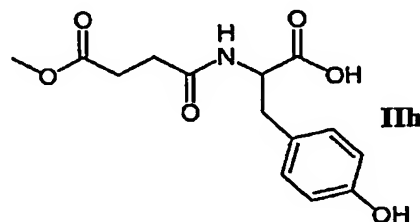
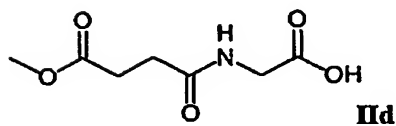
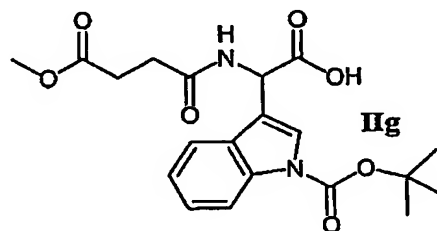
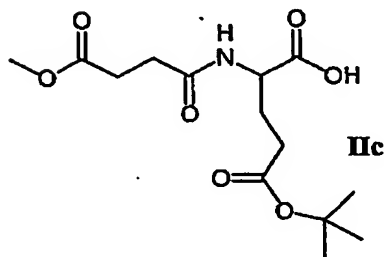
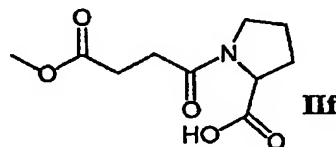
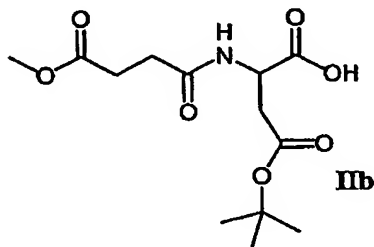
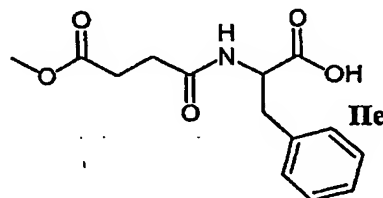
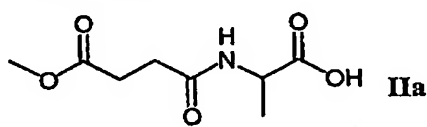
HBTU (105mg, 0.28mmol) was added to a stirring solution of acid (**IIa-IIr**) (0.23mmol), DIPEA (0.1ml, 0.58mmol) and DMF (2ml) at RT under a nitrogen atmosphere. After 5 mins, amine (**1**) (100mg, 0.24mmol) was added and the reaction mixture stirred for 2h. Chloroform (15ml) was added to the reaction mixture, which was washed successively with 10% citric acid (2x15ml),

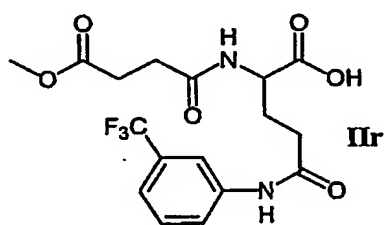
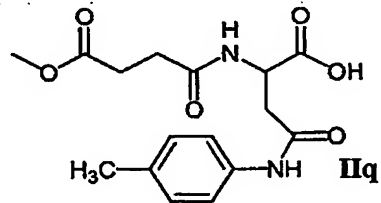
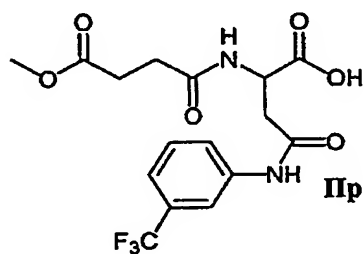
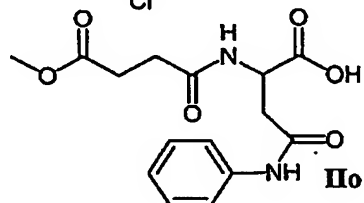
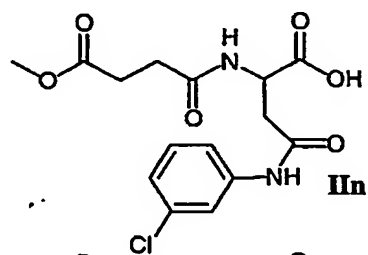
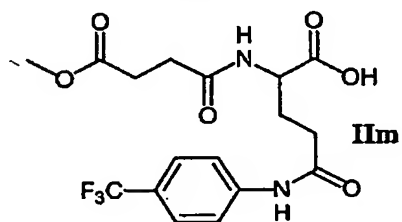
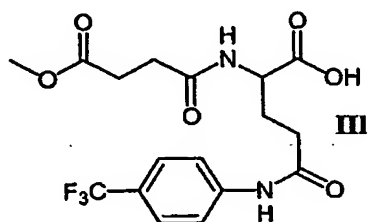
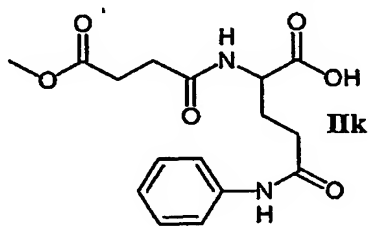
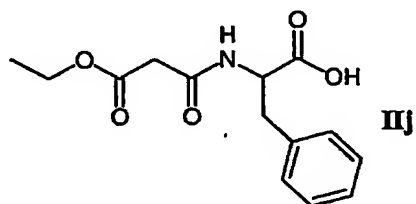
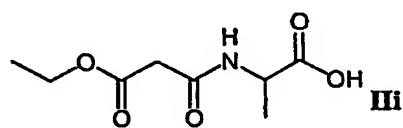
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saturated aqueous sodium bicarbonate (2x15ml) and brine (2x15ml). Drying, filtering and concentration under reduced pressure afforded the crude residue (3A-S) (approximately 150-200mg) that was used directly in the next reaction.

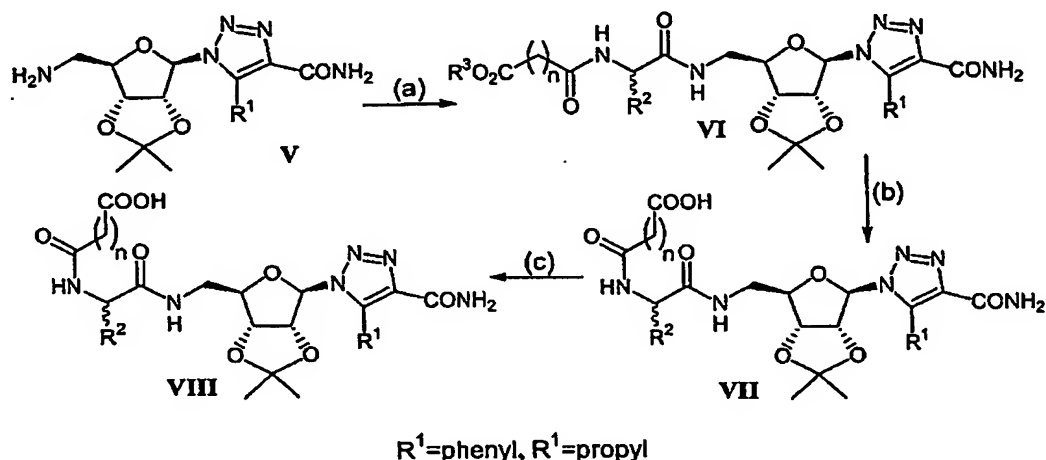
5 **Step (ii)**

A mixture of the crude residues (designated by general structure **III**) and potassium hydroxide (15 equivalents ; dissolved in 1 ml of water) in MeOH (1ml) was stirred at RT overnight. The reaction mixture was acidified to pH 4-5 with amberlite IR-120 ion exchange resin, filtered and concentrated under reduced pressure. The residue was treated with 90/10 TFA-H₂O (2ml) for 15 minutes at RT followed by concentration under reduced pressure (co-evaporating with acetonitrile). Purification using reverse phase C-18 HPLC using a solvent gradient of water/acetonitrile afforded the desired product (designated by general structure **IV**) as white solids (10-30mg).





Example 2: General Scheme for the Solution Phase Synthesis of a Ribofuranosyl-Triazole Based Library



5

Conditions: (a) HBTU (1.2eq.), DIPEA (2.5eq.), DMF; (b) LiOH (2eq.), THF, H₂O, r.t., o/n; (c) 90% TFA/H₂O, r.t., 15mins.

General Procedures For Solution Phase Library Preparation in Example 2.

10 Method 1

To a solution of an acid selected from **IIa-r** (selected for $n=2$ in above scheme) in DMF (0.3 ml, 0.35 M, 1.0 equiv.) at room temperature was added a solution of HBTU in DMF (0.3 ml, 0.42 M, 1.2 equiv.) followed by DIPEA (2.5 equiv.). After 10 min., a solution of sugar amine **V** in DMF (0.3 ml, 0.37 M, 1.05 equiv.) was added. The resulting solution was stirred at room temperature for 2.5 h, then diluted with DCM (8 ml) and washed with 10 % citric acid (2 x 5 ml), saturated NaHCO₃ (2 x 5 ml), brine (5 ml) and water (5 ml). The solvent was removed in vacuo.

20 Method 2

A solution of the sugar amine **V** in DMF (0.3 ml, 0.37 M, 1.05 equiv.) was added to a solution of an acid selected from **IIa-r** (selected for $n=1$ in the above scheme) in DMF (0.3 ml, 0.35 M, 1.0 equiv.). To this solution was added a solution of HBTU in DMF (0.3 ml, 0.42 M, 1.2 equiv.) followed by DIPEA (2.5 equiv.) at room temperature. The resulting solution was stirred at

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room temperature for 2.5 h, then diluted with DCM (8 ml) and washed with 10 % citric acid (2 x 5 ml), saturated NaHCO₃ (2 x 5 ml), brine (5 ml) and water (5 ml). The solvent was removed in vacuo affording a range of ribofuranosyl dipeptide ester conjugates VI.

5

Each dipeptide ester VI was then dissolved in THF (0.5 ml) and treated with a solution of lithium hydroxide in water (0.5 ml, 0.45 M, 2.1 equiv.). The resulting mixture was stirred at room temperature overnight, then evaporated to dryness under reduced pressure to provide ribofuranosyl dipeptide acids VII.

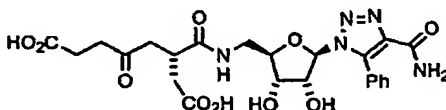
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Final Products VIII

Each dipeptide acid VII was dissolved in 90 % TFA / water (1.0 ml) and the resulting solution was stirred at room temperature for 15 min. then acetonitrile was added and the solution was concentrated in vacuo. The final products

15 VIII were freeze dried and purified by HPLC.

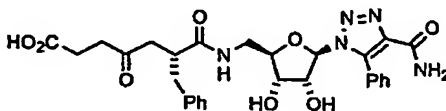
¹H-NMR Characterisation of Selected Library Members of Example 10.



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δ_H (400 MHz: D₂O) 2.36-2.55 (m, 5H, alkyl H), 2.57-2.76 (m, 1H, alkyl H), 3.31-3.48 (m, 2H, H5), 3.98-4.07 (m, 1H, H4), 4.45-4.56 (m, 2H, H3, NCHCO), 4.69-4.75 (m, 2H, H2), 5.57 (d, *J* 2.4 Hz, 1H, H1), 7.32-7.40 (m, 2H, PhH), 7.41-7.53 (m, 3H, PhH).

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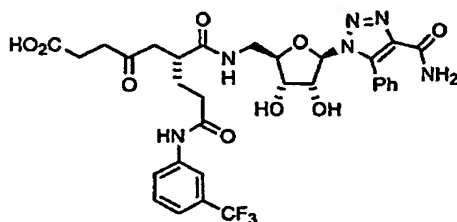


δ_H (400 MHz: D₂O) 2.26-2.40 (m, 4H, alkyl H), 2.73 (dd, *J* 14.0, 8.0 Hz, 1H, CHaPh), 2.88 (dd, *J* 14.0, 6.2 Hz, 1H, CHbPh), 3.30 (dd, *J* 14.6, 4.6 Hz, 1H,

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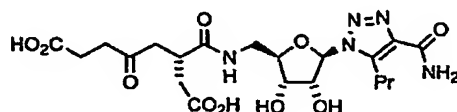
H5a), 3.42 (dd, J 14.6, 3.8 Hz, 1H, H5b), 3.96-4.02 (m, 1H, H4), 4.26 (t, J 5.8 Hz, 1H, H3), 4.36 (t, J 7.4 Hz, 1H, NCHCO), 5.52 (d, J 2.8 Hz, 1H, H1), 7.02-7.20 (m, 5H, PhH), 7.35 (d, J 6.4 Hz, 2H, PhH), 7.42-7.54 (m, 3H, PhH).

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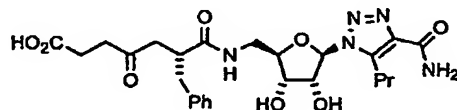
δ_H (400 MHz: D_2O) 1.76-1.87 (m, 1H, alkyl H), 1.96-2.08 (m, 1H, alkyl H), 2.30-2.41 (m, 6H, alkyl H), 3.43 (d, J 4.4 Hz, 2H, H5), 4.06 (q, J 5.2 Hz, 1H, H4), 4.26 (dd, J 9.0, 5.2 Hz, 1H, H3), 4.40 (t, J 5.6 Hz, 1H, NCHCO), 4.69-4.74 (m, 1H, H2), 5.54 (d, J 3.2 Hz, 1H, H1), 7.2.8-7.48 (m, 8H, PhH), 7.65 (s, 1H, PhH).

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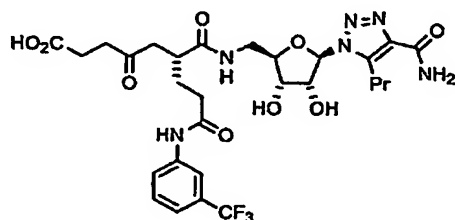


δ_H (400 MHz: D_2O) 0.77 (t, J 7.4 Hz, 3H, CH_2CH_3), 1.42-1.56 (m, 2H, CH_2CH_3), 2.37-2.53 (m, 5H, alkyl H), 2.58 (dd, J 15.4, 5.4 Hz, 1H, alkyl H), 2.89 (t, J 7.6 Hz, 2H, $ArCH_2$), 3.30-3.46 (m, 2H, H5), 4.07-4.15 (m, 1H, H4), 4.42-4.53 (m, 2H, H3, NCHCO), 4.70-4.75 (m, 2H, H2), 5.87 (d, J 2.8 Hz, 1H, H1).

25



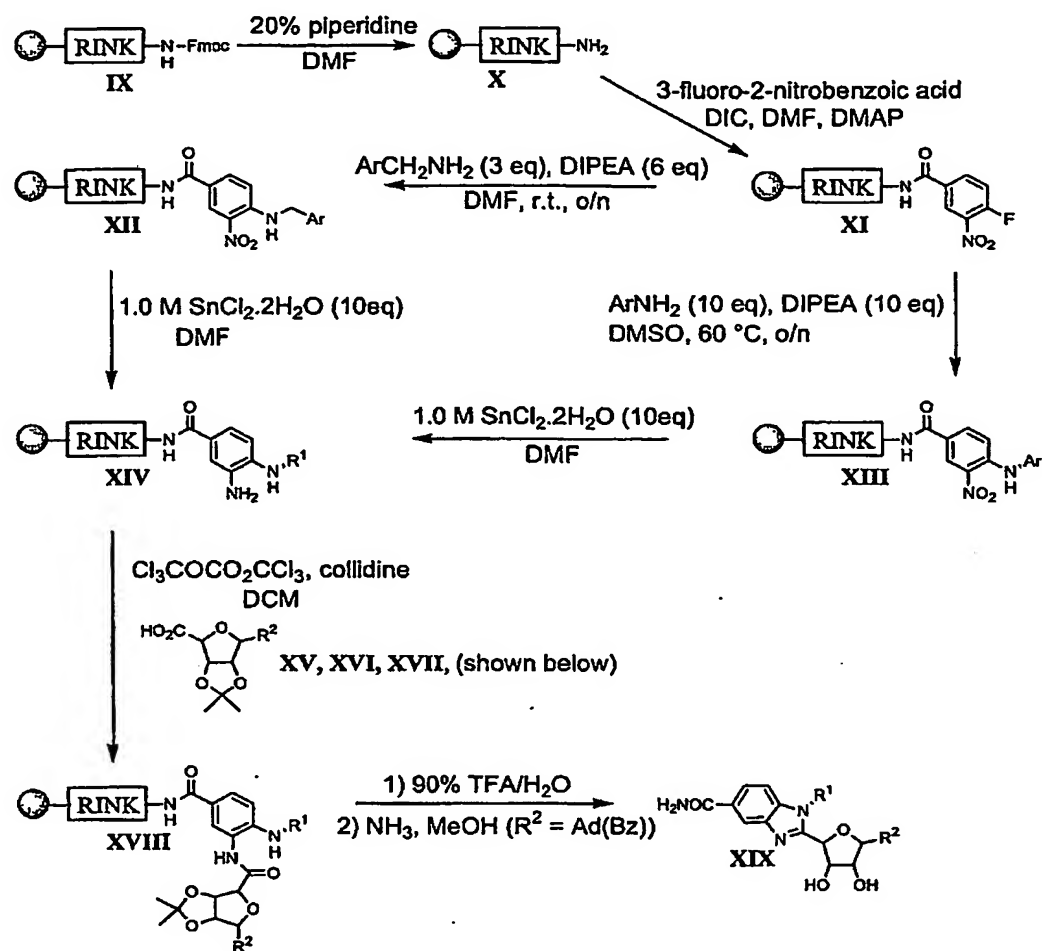
δ_H (400 MHz: D₂O) 0.78 (t, J 7.2 Hz, 3H, CH₂CH₃), 1.38-1.46 (m, 2H, CH₂CH₃), 2.34 (bs, 4H, alkyl H), 2.70 (t, J 10.2 Hz, 1H, ArCH_a), 2.74-2.96 (m, 3H, ArCH_b, CH₂Ph), 3.25-3.45 (m, 2H, H5), 4.02-4.12 (m, 1H, H4), 4.18-4.25 (m, 2H, H3), 4.29-4.38 (m, 1H, NCHCO), 5.83 (bs, 1H, H1), 6.99-7.20 (m, 5H, PhH).



10 δ_H (400 MHz: D₂O) 0.73 (t, J 7.4 Hz, 3H, CH₂CH₃), 1.36-1.50 (m, 2H, CH₂CH₃), 1.73-1.85 (m, 1H, alkyl H), 1.88-2.03 (m, 1H, alkyl H), 2.28-2.45 (m, 6H, alkyl H), 2.84 (q, J 7.5 Hz, 2H, ArCH₂), 3.42 (d, J 4.4 Hz, 2H, H5), 4.10-4.20 (m, 2H, H3, H4), 4.38 (t, J 5.4 Hz, 1H, NCHCO), 5.84 (d, J 2.8 Hz, 1H, H1), 7.34-7.52 (m, 3H, ArH), 7.65 (s, 1H, ArH).

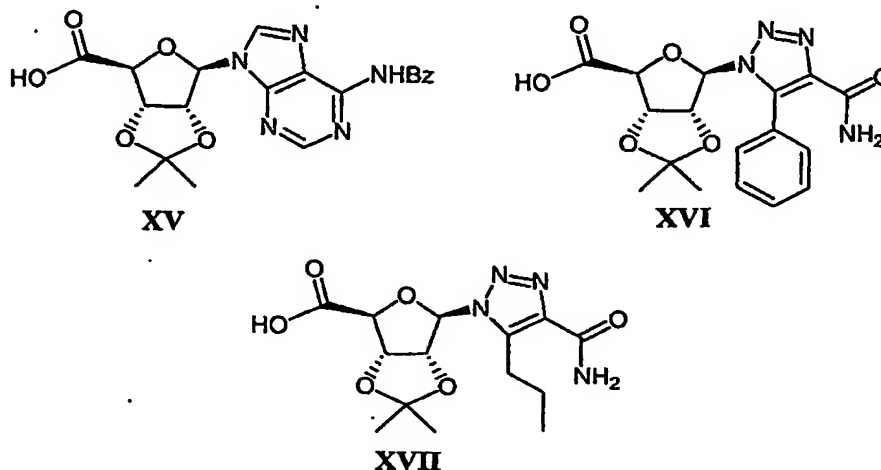
15

Example 3: Solid Phase Synthesis of Libraries Employing Ribouronic Acid Building Blocks.



5

Blocks XV, XVI and XVII

**Resin X**

5 Rink-amide resin **IX** (12 g, 0.7 mmol/g, 8.4 mmol) was washed with DMF (2 x 120 ml), then treated with 20 % piperidine in DMF (120 ml) and shaken at r.t. for 30 min. The resin was drained and washed with DMF (2 x 120 ml). The reaction was repeated and the resin was drained, washed with DMF (2 x 120 ml), DCM (2 x 120 ml), MeOH (2 x 120 ml) and ether (2 x 120 ml), and dried in vacuo for 2 h. The Fmoc test was negative.

10

Resin XI

Resin **X** was washed under N₂ with dry DCM (1 x 80 ml, 1 x 60 ml). To a solution of 4-fluoro-3-nitrobenzoic acid (9.3 g, FW 185.09, 50.2 mmol, 6 equiv.) in dry DCM (60 ml) and dry DMF (9 ml) at r.t. and under N₂ was added
 15 1,3-diisopropylcarbodiimide (DIC, 3.9 ml, d 0.806, FW 126.20, 24.9 mmol, 3 equiv.). The solution was stirred for 10 min., then added to the resin followed by 4-(dimethylamino)pyridine (DMAP, 102 mg, FW 122.17, 0.83 mmol, 0.1 equiv.). The resin was then shaken at r.t. for 3 h, drained, washed with DMF (4 x 120 ml), DCM (3 x 120 ml) and ether (2 x 120 ml), and dried in vacuo o/n.
 20 The ninhydrin test was only very slightly positive (light blue resin and yellow solution).

Resins XII

Resin XI (200 mg, 0.14 mmol) was washed under N₂ with dry DMF (2 ml), then treated with a solution of amine (0.42 mmol, 3 equiv.) and diisopropylamine (DIPEA, 0.146 ml, d 0.742, FW, 129.25, 0.84 mmol, 6 equiv.) in dry DMF (2 ml) and shaken at r.t. o/n. The resin was drained and
 5 washed with DMF (3 x 2 ml) and DCM (3 x 2 ml).

Resins XIII

Resin XI (200 mg, 0.14 mmol) was washed under N₂ with dry DMSO (2 ml), then treated with a solution of aniline (1.40 mmol, 10 equiv.) and
 10 diisopropylamine (DIPEA, 0.244 ml, d 0.742, FW, 129.25, 1.40 mmol, 10 equiv.) in dry DMSO (2 ml) and shaken at 60 °C o/n. The resin was drained and washed with DMF (3 x 2 ml) and DCM (3 x 2 ml).

Resins XIV

15 Resin XII or XIII (0.14 mmol) was washed with DMF (2 x 2 ml) and then DMF (0.7 ml) followed by a solution of SnCl₂·2H₂O in DMF (0.7 ml, 2 M, 1.40 mmol, 10 equiv.) were added. The resin was shaken at r.t. o/n, then washed with DMF (5 x 2 ml), DCM (3 x 2 ml) and MeOH (5 x 2 ml).

20 *Resins XVIII*

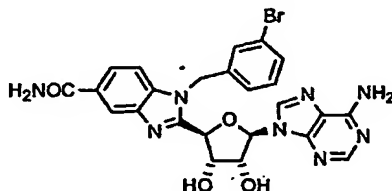
Resin XIV (0.14 mmol) was washed with DCM (2 x 2 ml) and then under N₂ with dry DCM (2 x 2 ml). A suspension of any of sugar-acid building blocks XV, XVI, or XVII (0.42 mmol, 3 equiv.) in dry DCM (2 ml) was treated with triphosgene (42 mg, FW 296.75, 0.14 mmol, 1 equiv.) followed by collidine
 25 (0.159 ml, d 0.917, FW 121.18, 1.20 mmol, 8.6 equiv.). An effervescence was observed and a solution formed. After 1 min., this solution was added to the resin and the resin was shaken at r.t. for 3 h. The resin was drained and washed with DCM (5 x 2 ml) and MeOH (3 x 2 ml).

30 *Final cleaved products XIX*

Resin G (0.14 mmol) was treated with 90 % TFA / water (2 ml) at r.t. o/n. The resin was drained and washed with acetonitrile (2 x 1.5 ml). The solvent was removed in vacuo. The adenosine-containing products were treated with saturated ammonia in methanol (4 ml) at r.t. o/n. The solvent was removed in

vacuo and the product was again treated with sat NH_3 in MeOH at r.t. o/n. The solvent was removed in vacuo.

Exemplary Compound

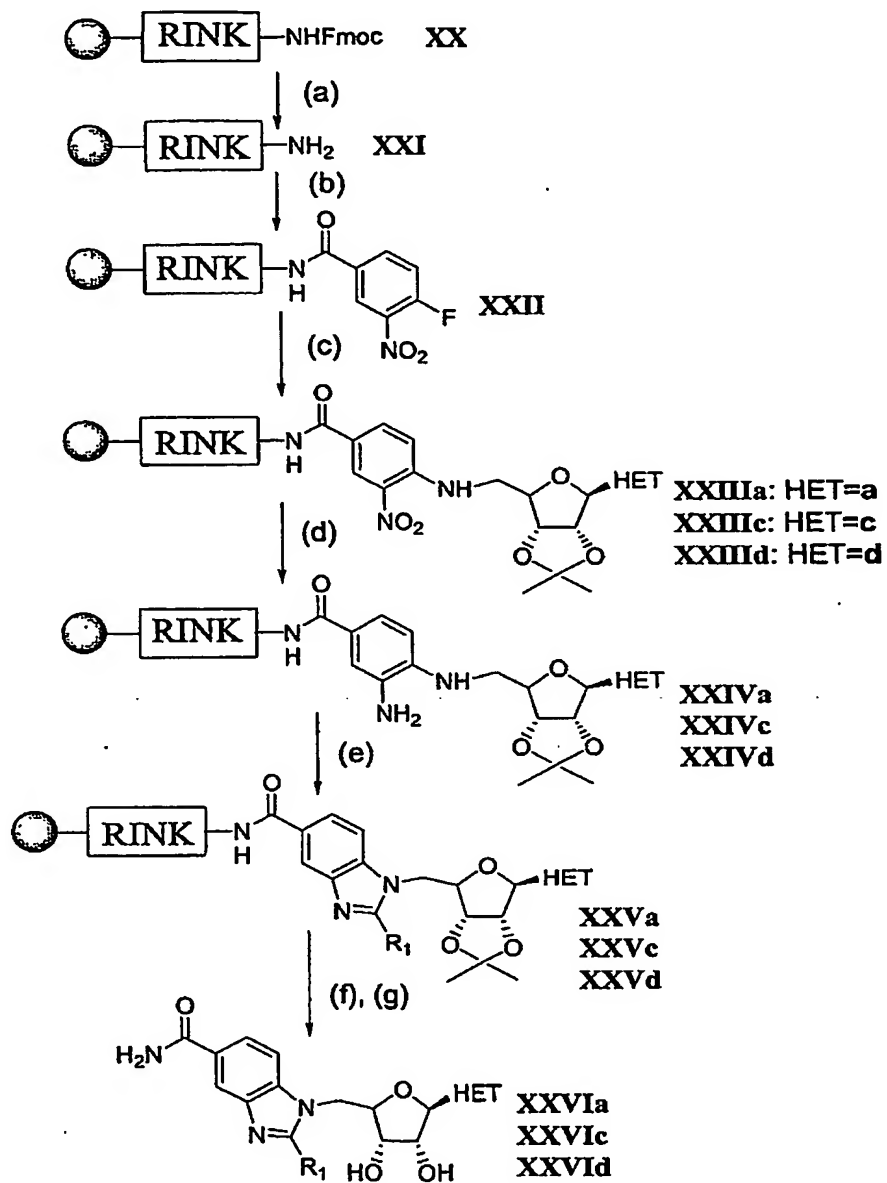


5

δ_{H} (400 MHz: d_6 DMSO) 4.92 (q, J 4.4 Hz, 1H, H2 or H3), 4.98 (q, J 5.1 Hz, 1H, H2 or H3), 5.33 (d, J 4.0 Hz, 1H, H4), 5.54 (d, J 16.8 Hz, 1H, CH_aPh), 5.62 (d, J 17.2 Hz, 1H, CH_bPh), 5.77 (d, J 5.3 Hz, 1H, OH), 5.80 (d, J 5.4 Hz, 1H, OH), 6.10 (d, J 5.3 Hz, 1H, H1), 6.96 (d, J 7.9 Hz, 1H, PhH), 7.09 (t, J 7.8 Hz, 1H, PhH), 7.24 (bs, 2H, NH_2), 7.27 (bs, 1H, PhH), 7.29 (s, 1H, CONH_a), 7.36 (d, J 8.9 Hz, 1H, PhH), 7.47 (d, J 8.3 Hz, 1H, ArH), 7.78 (dd, J 8.5, 1.6 Hz, 1H, ArH), 7.98 (bs, 2H, ArH, CONH_b), 8.31 (d, J 1.2 Hz, 1H, ArH), 8.37 (s, 1H, ArH).

15

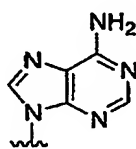
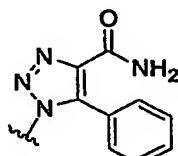
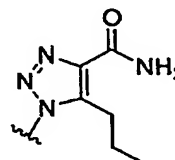
Example 4: Solid Phase Synthesis of a Benzimidazole Ribofuranosyl Library.



- 5 **Conditions:** (i) 20% Piperidine/DMF; (ii) 4-F-3-NO₂-Benzoic Acid, DIC, DMAP, DMF; (iii) Sugar Amine, DIPEA, DMF; (iv) (SnCl₂·H₂O, DMF; (v) R¹CHO, NMP; (vi) NH₂NH₂, DMF; (vii) (a) 50% TFA/DCM, (b) TFA/MeCN/H₂O.

Heterocycles (HET) for Example 12 are listed below. Heterocycle **a** refers to substances **XXIIIa-XXVIa** (heterocycle from building block **2**), heterocycle **c** refers to substances **XXIIIc-XXVIc** (heterocycle from building block **20**) and heterocycle **d** refers to substances **XXIIIId-XXVIId**.

5

**a****c****d**

Resin XXI (carried out in Triplicate)

- Rink amide resin **XX** (4g, 0.7mmol/g, 2.8mmol) was washed with DMF
 10 (2x40mL) then treated twice with 20% piperidine /DMF (40mL) for 20 mins.
 The resin was filtered, washed with DMF (4x40mL), DCM (4x40mL), MeOH
 (4x40mL) and ether (2x20ml) followed by drying *in vacuo* for 1h.

Resin XXII (carried out in triplicate)

- 15 4-Fluoro 3-nitrobenzoic acid (3.1g, 16.8mmol) was dissolved in dry DCM
 (20mL) and dry DMF (3mL). DIC (1.3mL, 8.4mmol) was added. The solution
 was stirred for 10 mins then added to resin **XX** pre-swollen in dry DCM,
 followed by DMAP (34 mg, 0.28mmol) The resin was shaken at rt for 3h then
 washed with DMF (4x40mL), DCM (4x40mL) and dried *in vacuo* overnight.

20

Resin XXIIIa-c

- Resin **XXII** was washed under N₂ with dry DMF (2 x 40 mL) then sugar amine
 building block (Block **1** : 1.37g, 3.4mmol ; Block **5a** : 1.22g, 3.4mmol ; Block
5b : 1.11g, 3.4mmol) and DIPEA (1mL, 5.6 mmol) in dry DMF (35mL) was
 25 added. The resin was shaken at r.t. overnight then washed with DMF
 (4x30mL), DCM (4x30mL) and dried *in vacuo* overnight.

Resin XXIVa,c,d

- Resins **XXIIIa,c,d** were washed with DMF (2x30mL) then swollen in DMF
 30 (14mL). A solution of 2M SnCl₂·2H₂O in DMF (14mL, 28mmol) was added and

the resin was shaken at rt for overnight. The resin was washed extensively with DMF (4x30mL), DMF/MeOH 1:1 (4x30mL), DCM (4x30mL), DCM/MeOH 1:1 (4x30mL), DCM (2x30mL) and dried *in vacuo* overnight. The reduction was repeated a second time on resins XXIIIc,d for 6 hours using the same conditions. Resin XXIIIa did not require a second cycle of reduction.

Resin XXVa,c,d

Resins XXIVa,c,d (approx. 200mg, 0.14mmol) were placed into test tubes. A solution of an aldehyde selected from XXVII-1 to XXVII-19 (5.0 equivalents) in NMP (4ml) was added to each test tube that was then shaken and placed in a 45-50°C graphite bath overnight. The resins were transferred to a SPOS plastic reaction vessel with MeOH with the resin subsequently washed with DMF (3x4mL), DCM (3x4mL), MeOH (3x4mL), ether (3x4mL) and dried *in vacuo* overnight. Resin XXIVa (approx. 200mg, 0.14mmol) was then further washed with DMF (2x3mL) and a solution of hydrazine (0.068ml, 1.4mmol, 10.0 equivalents) in DMF (1.4ml ; 1M wrt hydrazine) was added. The resin was shaken overnight, filtered and washed with DMF (3x2mL), DCM (3x2mL), DCM-MeOH 1:1 (3x2mL), DCM (3x2mL) and dried *in vacuo* overnight.

Cleavage Procedure

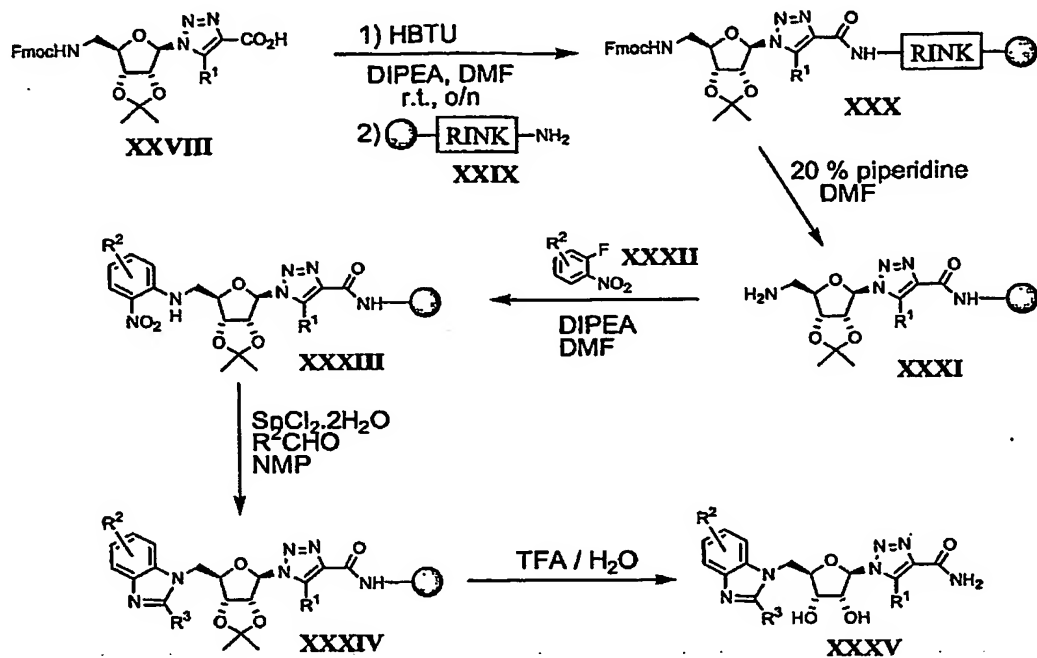
Resins XXVc,d (approx. 200mg) were washed with DCM (2x 2mL) then treated with TFA/DCM 1:1 (1mL) for 15 mins. The resin was filtered and washed with CH₃CN (1ml) (filtrates collected). This procedure was repeated for a second cycle. The filtrates had DCM removed by blowing N₂ into the sample tubes for 2h. Each of the sample tubes had water (1ml) added followed by shaking/stirring for 3h. Solvent evaporation was carried out by passing N₂ into the sample tubes to afford the crude products XXVIa,c,d.

Exemplary Aldehydes used in Example 12.

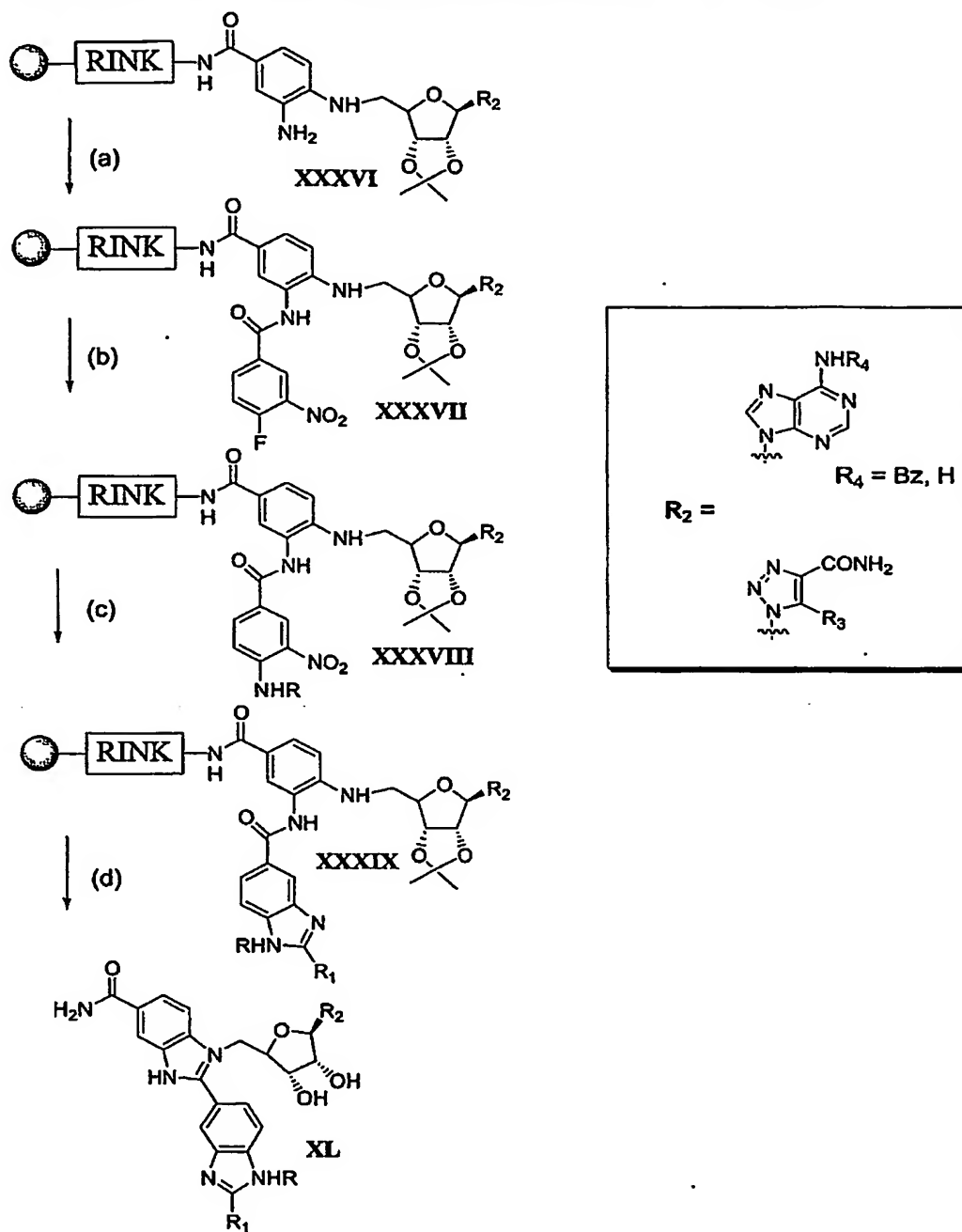
No.	Aldehyde
XXVII-1	benzaldehyde
XXVII-2	3-Bromobenzaldehyde
XXVII-3	m-Tolualdehyde
XXVII-4	2-Methoxybenzaldehyde
XXVII-4	p-Tolualdehyde
XXVII-5	4-Dimethylaminobenzaldehyde
XXVII-6	4-Cyanobenzaldehyde
XXVII-7	1,2,3,6-tetrahydrobenzaldehyde
XXVI-8	Indole-3-carboxaldehyde
XXVII-9	2-naphthaldehyde
XXVI-10	3-methyl thiophene-2-carboxaldehyde
XXVII-11	cyclohexane carboxaldehyde
XXVII-12	pyrrole-2-carboxaldehyde
XXVII-13	phenyl acetaldehyde
XXVII-14	4-(2-pyridyl)benzaldehyde
XXVII-15	a,a,a-trifluoro-o-tolualdehyde
XXVII-16	2,5-dimethylbenzaldehyde
XXVII-17	3,5-difluorobenzaldehyde
XXVII-18	2-fluorobenzaldehyde
XXVII-19	4-fluoro-3-(trifluoromethyl)benzaldehyde

Examples 5: Solid Phase Synthesis of a Imidazole-Ribofuranosyl Triazole

Library

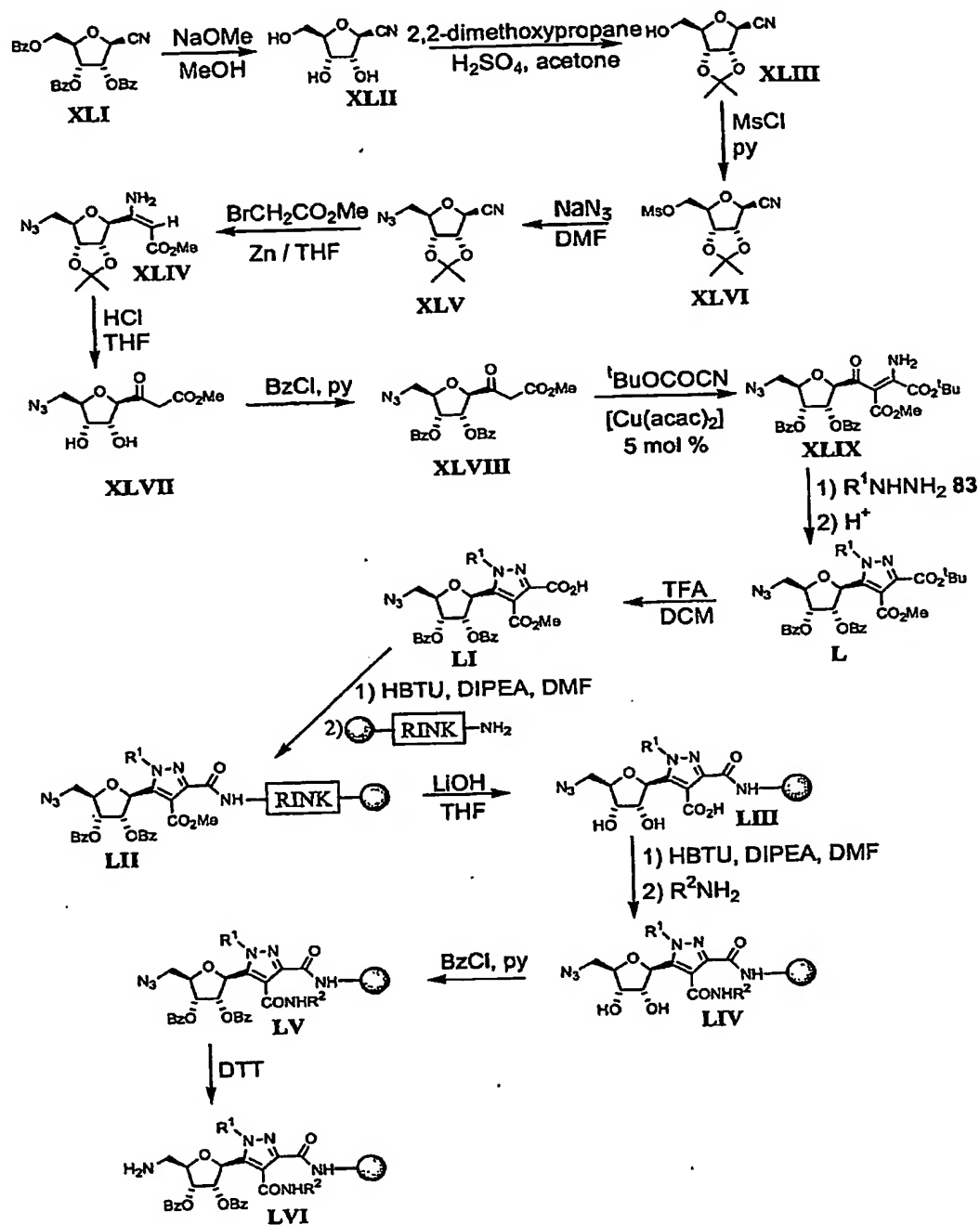


Example 6: Solid Phase Synthesis of a Bis-Benzimidazole Library

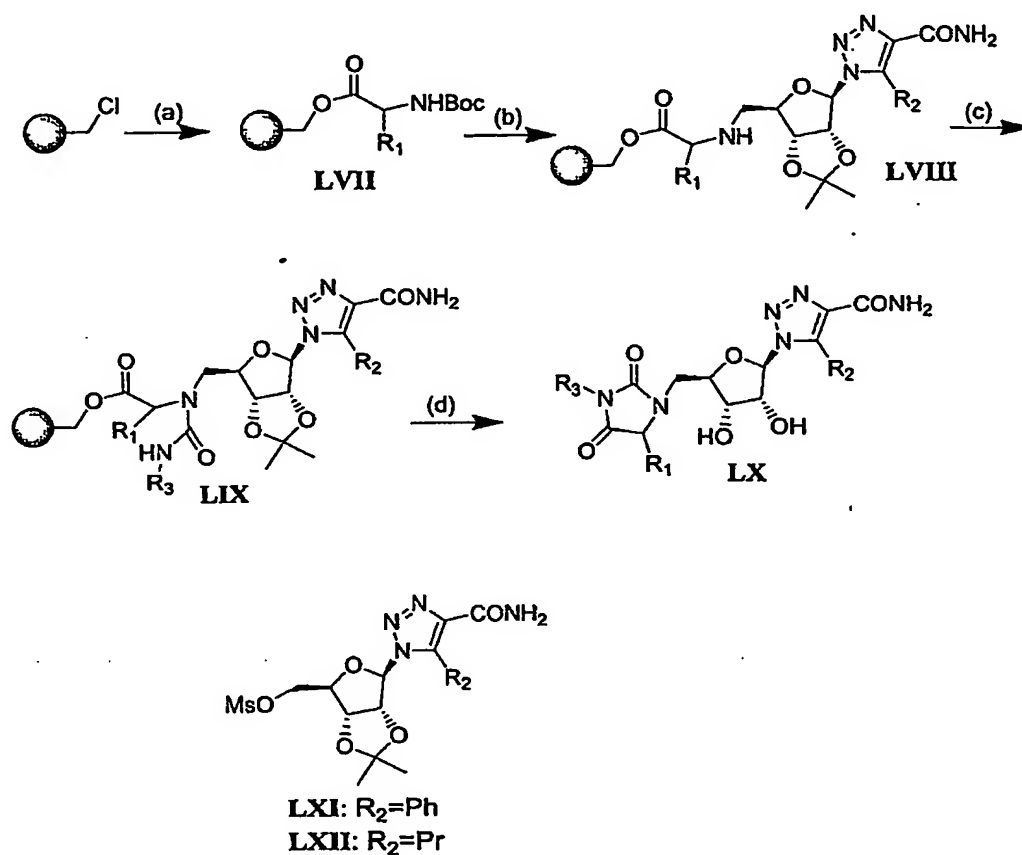


Conditions: (a) 4-F-3-NO₂-Benzoic Acid, DMF-DCM; (b) RNH₂, DIPEA, DMF; (c) SnCl₂·2H₂O, R¹CHO, NMP; (d) 100% TFA

Example 7: Solid Phase Synthesis of a library via a cyano building block



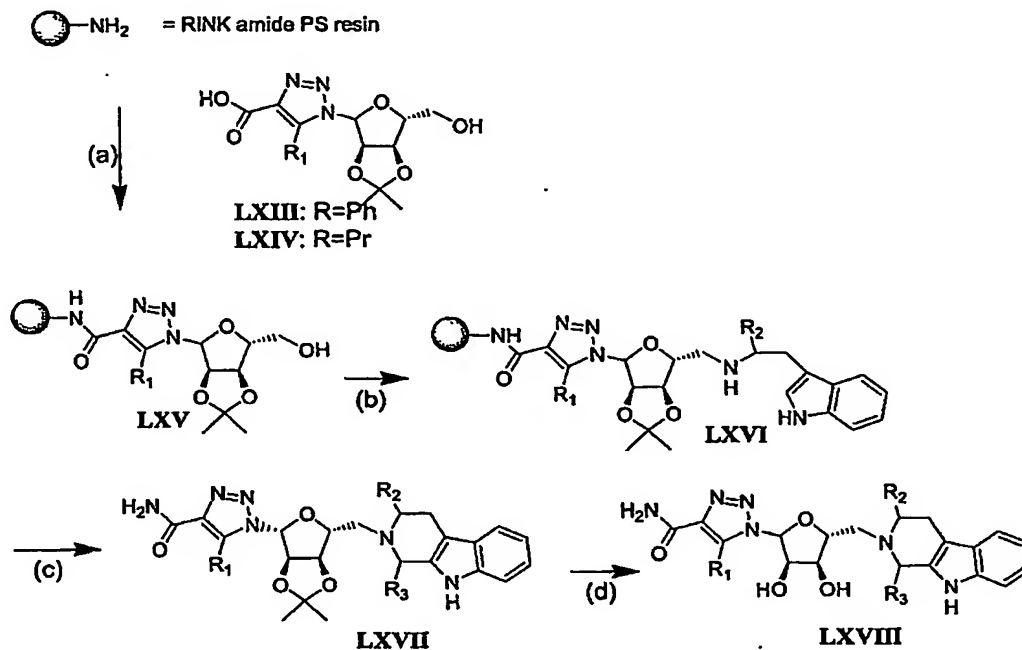
**Example 8: Solid Phase Preparation of a Library of Hydantoin Ribofuranosyl
Triazoles.**



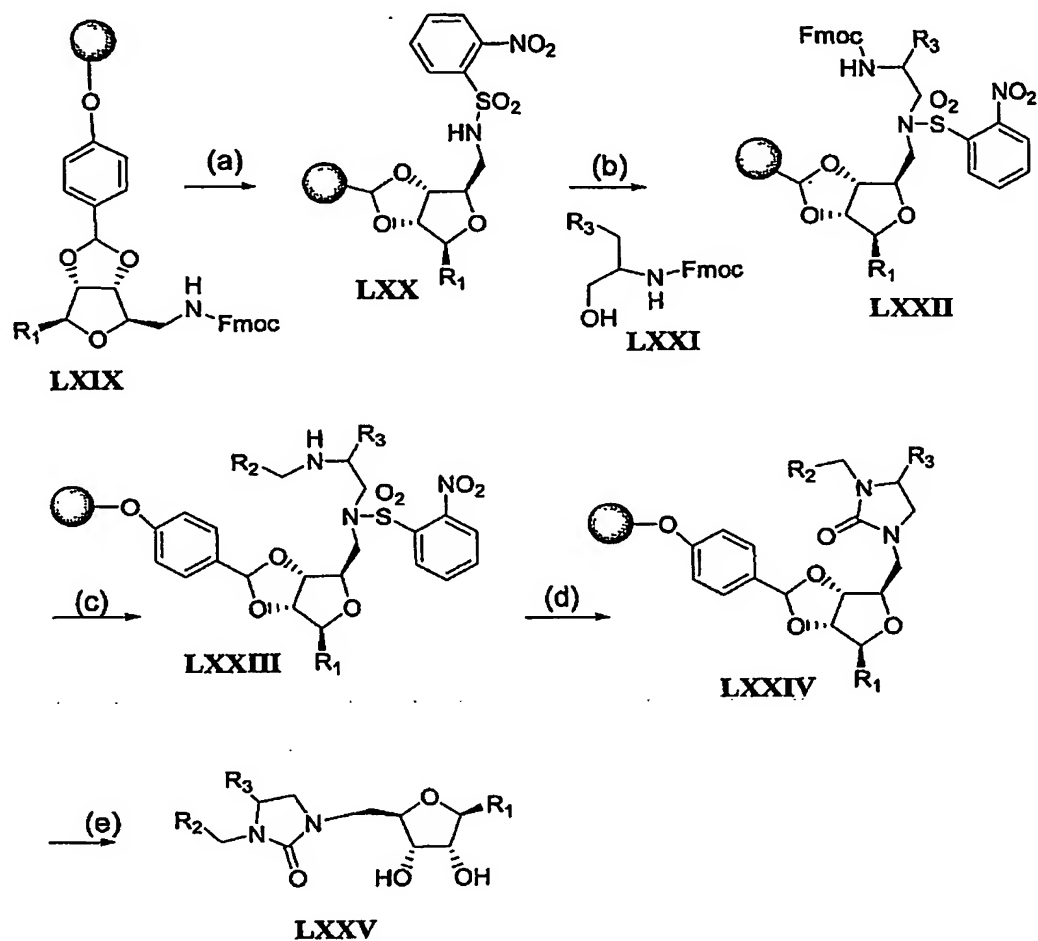
5

Conditions: (a) CsO₂C-CH(R₁)-NHBoc, DMF, 50°C, 12h; (b) (i) TFA, 10mins, (ii) DIEA, DMF, 16 or 17, 12h; (c) (i) Triphosgene, DIEA, DCM, 1h, (ii) R₃NH₂, DIEA, DCM, 1h; (d) (i) TFA, H₂O, DCM, 1h, (ii) MeOH/Net₃ - 1:1, 60°C, 12h.

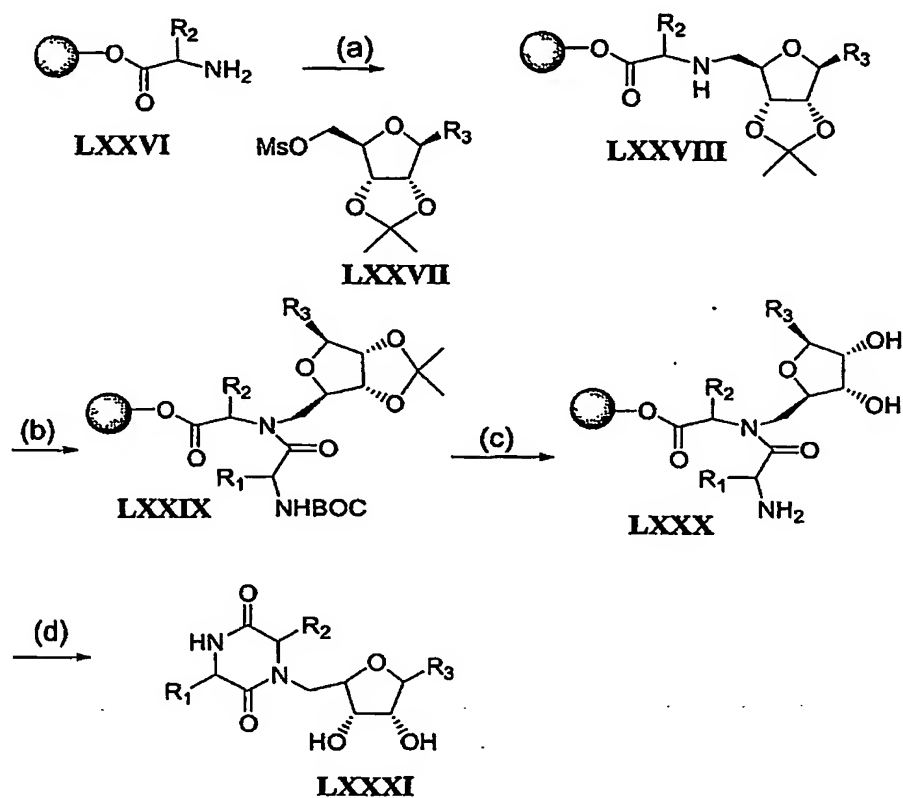
10

Example 9: Synthesis of a Library of beta-Carbolines.

- 5 **Conditions:** (a) 1eq. HBTU, 2eq. DIEA, DMF, rt, 2h; (b) (i) MsCl, DCM, (ii) Tryptamine derivative, DMF (c) $R_3\text{CHO}$, 25% TFA/DCM, rt; (d) TFA/ H_2O - 1:1.

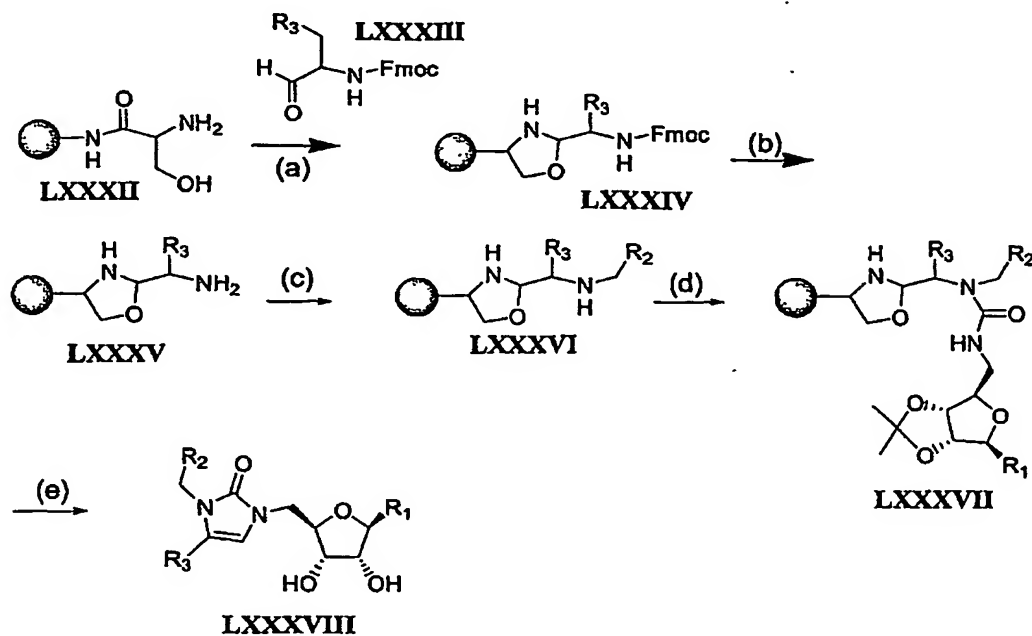
Example 10: Synthesis of a library of cyclic ureas

- 5 **Conditions:** (a) (i) 20% piperidine/DMF, (ii) O-NBS-Cl, DCM; (b) PPh₃, aminoalcohol, DEAD, (c) (i) 20% piperidine in DMF, (ii) R₂-CHO, TMOF/THF, NaCNBH₃; (d) (i) Na⁺PhS⁻, DMF, (ii) triphosgene, DCM, DIEA, (e) TFA/H₂O.

Example 11: Synthesis of a library of diketopiperazines

- 5 **Conditions:** (a) compound **LXXVII**, DMF, DIEA; (b) BOC-amino acid (4eq.), DIC (2 eq.), DCM; (c) TFA, H₂O, 1h at 50°C; (d) reflux in toluene.

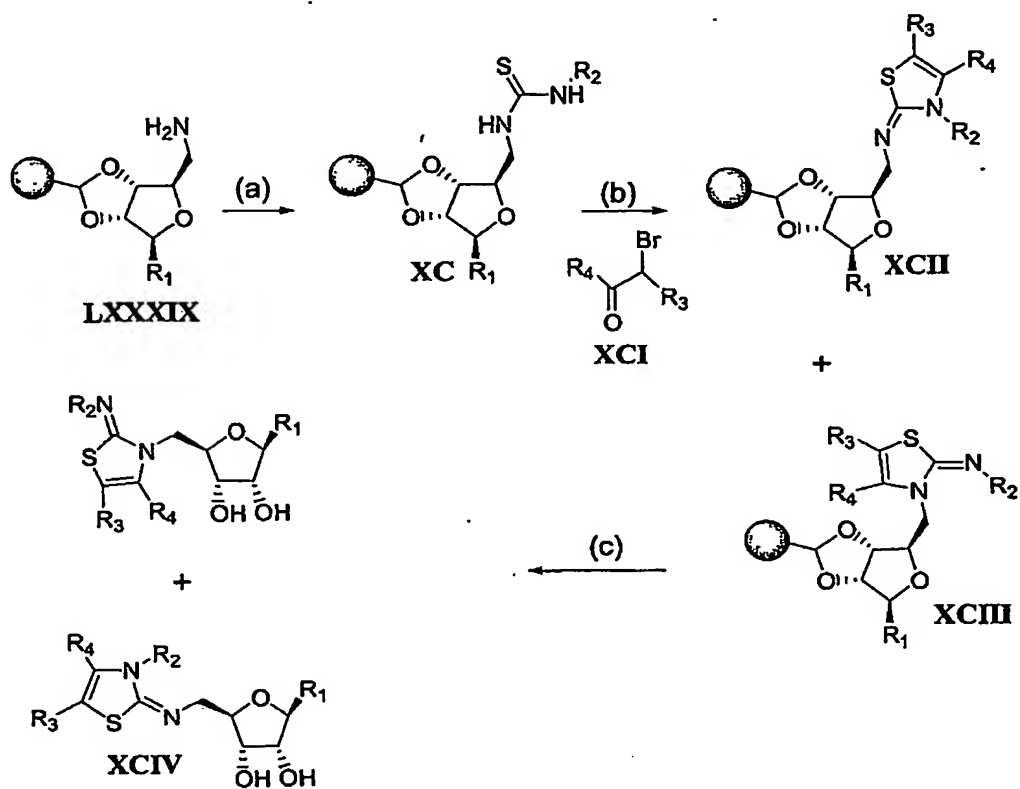
Example 12: Synthesis of a library of Imidazol-2-ones



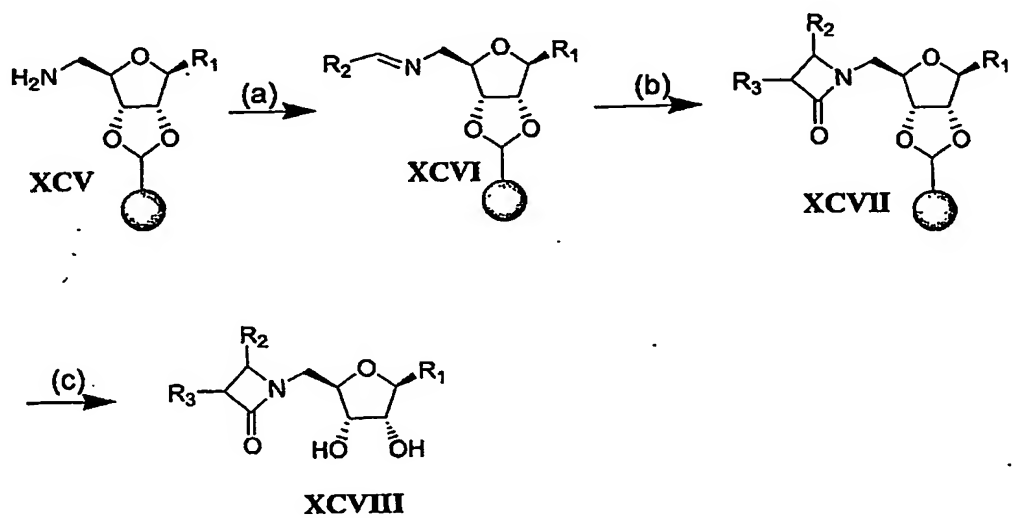
5 Conditions: i. aldehyde, TMOF/THF; ii. 20% piperidine in DMF; iii. R₂-CHO, NaCNBH₃; iv. a) triphosgene, 1h; b) aminosugar 1; v. TFA/H₂O.

Conditions: (a) aldehyde, TMOF/THF; (b) 20% piperidine/DMF; (c) R₂-CHO, NaCNBH₃; (d) (i) Na⁺PhS⁻, DMF, (ii) triphosgene, DCM, DIEA; (e) TFA/H₂O

Example 13: Synthesis of a library of 2-imino-dihydrothiazolidines

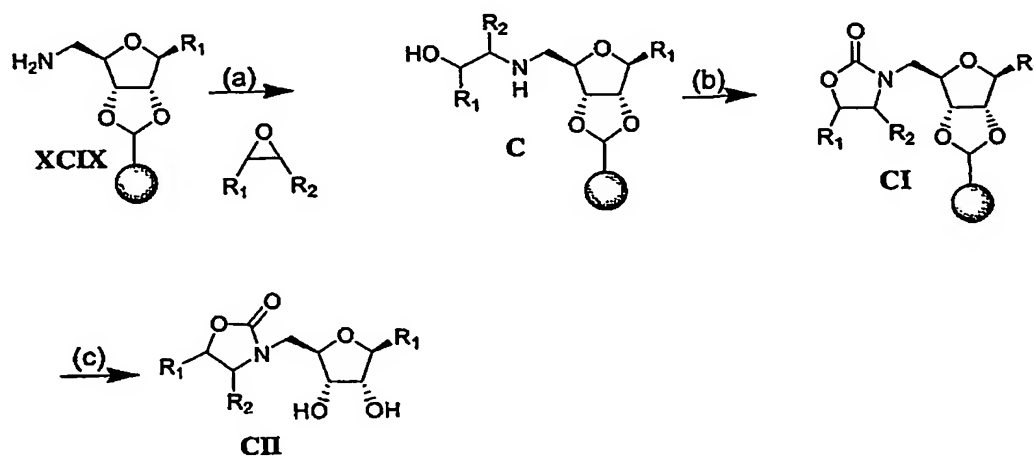


5 **Conditions:** (a) Isothiocyanate, DCM; (b) Bromoketone, DMF; (c) TFA/H₂O

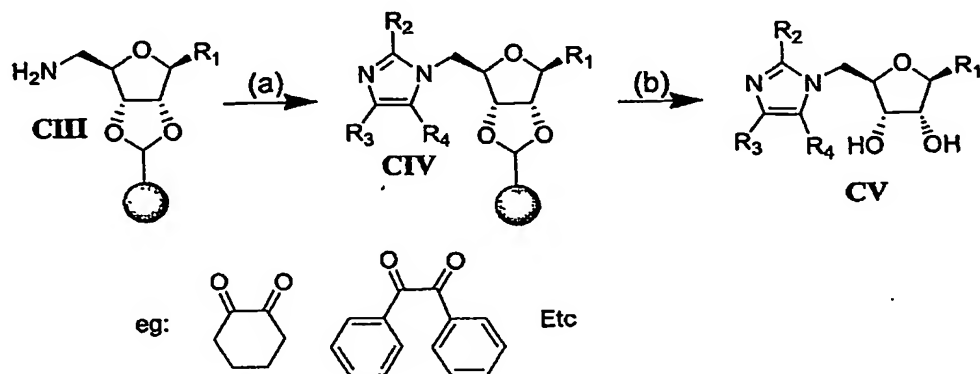
Example 14: Synthesis of a library of beta-lactams

5 Conditions: (a) R_2CHO , TMOF, THF; (b) R_3COCl , NEt_3 ; (c) TFA/ H_2O .

Example 15: Synthesis of a library of cyclic carbamates

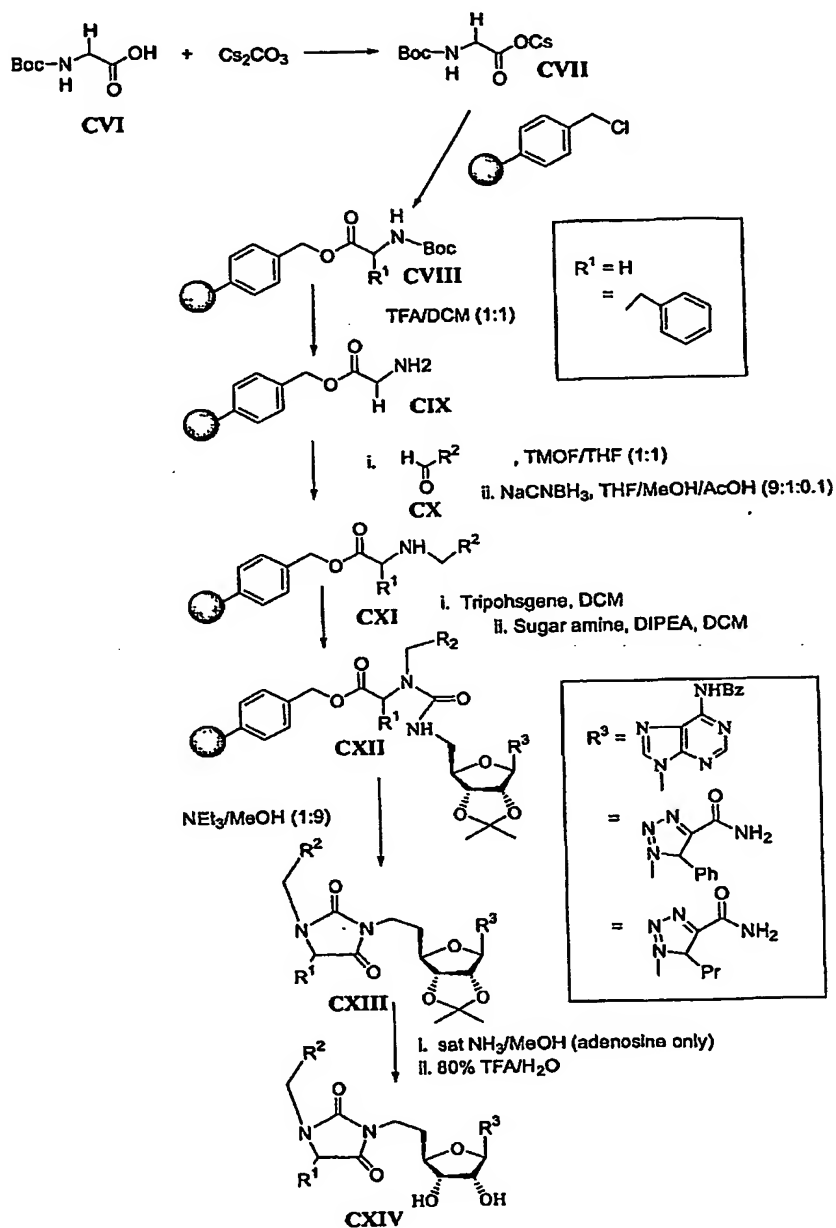


5 **Conditions:** (a) Epoxide, DIEA, DMF; (b) CDI, DCM; (c) TFA/H₂O.

Example 16: Synthesis of a library of imidazoles

5 Conditions: (a) $R_3\text{-CO-CO-R}_4$, NH_4OAc , $R_2\text{-CHO}$; (b) $\text{TFA}/\text{H}_2\text{O}$

Example 17 : Synthesis of a library of hydantoins



5

1. **Resin loading:** The cesium salt of the amino acid is made by dissolving the amino acid in methanol (5ml/mmol) and water (0.5ml/mmol) and

adding an aqueous solution of 20% Cs_2CO_3 until pH 7 is reached. The solvent is removed *invacuo* and the material is freeze-dried overnight to give a white powder. The resin is treated with the cesium salt (5eq) in dry DMF (4ml/g of resin) and stirred at 50°C for 24 hours. The resin is drained and washed with DMF, DMF/ H_2O (1:1; x 3), MeOH/ H_2O (1:1; x 3) and MeOH (x 3) and then dried *invacuo*.

2. *Boc-deprotection*: The resin is swelled in DCM and DCM/TFA (1:1) (5ml/g) added and the resin shaken for 15 min. The resin is drained and washed with DCM (x 2) and the process repeated. The resin is treated with 10% DIPEA/DCM and shaken for 2 minutes, washed with DCM (x 3) and dried *invacuo*.
3. *Reductive Amination*: 6 eq of aldehyde is dissolved in TMOF/THF (1:1; 2ml) and added to the resin (200mg) and shaken at room temperature for 3-4 hours. The resin is drained and a solution of NaCNBH_3 (2eq) in THF/MeOH/AcOH (9:1:0.1; 1ml) is added to the resin and shaken overnight at room temperature. The resin is then drained and washed with THF/MeOH (1:3; x 3), DMF/MeOH (1:3; x 3), DCM/MeOH (1:3; x 3) and DCM.
4. *Triphosgene/Sugar reaction*: In the gloved box, the resin is swelled in 10% DIPEA/DCM, a solution of triphosgene (1.5eq in 1.2ml of dry DCM) was added to the resin in two batches (gas generation causes resin to come out of syringes if added in one batch) and shaken for 1 hour. The resin is washed with dry DCM (1ml x 2) and a solution of the sugar amine (1.1eq) and DIPEA (2.2eq) in 1.5ml of dry DCM was added and shaken for 30 minutes. The resin is drained and washed with DMF (x 3), DCM (x 3) and MeOH (x 3) and dried.
5. *Cyclisation/Cleavage*: The resin was treated with a solution of MeOH/ NEt_3 (9:1; 2ml) and heated to 60°C overnight. The resin is drained, (collecting the filtrate) and washed with MeOH, (1ml), DCM

(1ml), MeOH (1ml) and DCM (1ml) and the solvent removed on the beta RVC (program 5). The process is then repeated.

5 6. *Benzoyl deprotection*: the crude material obtained by cyclisation is treated with saturated NH_3/MeOH (1ml) at room temperature, overnight. The solvent is then removed *invacuo*.

10 7. *Acetal deprotection*: The product was treated with 80% TFA/ H_2O (1ml), for 4 hours at room temperature. The solvent is removed *invacuo*.

Amino Acids – R¹

Phenylalanine

15 Glycine

Aldehydes – R²

Ald. No.	Aldehyde Name
CX-1	benzaldehyde
CX-2	2-Chlorobenzaldehyde
CX-3	3-Bromobenzaldehyde
CX-4	4-Fluorobenzaldehyde
CX-5	o-Tolualdehyde
CX-6	3-(Trifluoromethyl)benzaldehyde
CX-7	2-Nitrobenzaldehyde
CX-8	2,4-Dichlorobenzaldehyde
CX-9	3-Chlorobenzaldehyde
CX-10	4-Bromobenzaldehyde
CX-11	4-Chlorobenzaldehyde
CX-12	m-Tolualdehyde
CX-13	4-(Trifluoromethyl)benzaldehyde
CX-14	3-Nitrobenzaldehyde
CX-15	4-Dimethylaminobenzaldehyde

CX-16	3-vinylbenzaldehyde
CX-17	4-Nitrobenzaldehyde
CX-18	p-Tolualdehyde
CX-19	3,4-Dichlorobenzaldehyde
CX-20	4-Tert-Butylbenzaldehyde
CX-21	4-Cyanobenzaldehyde
CX-22	4-Biphenylcarboxaldehyde
CX-23	Octylaldehyde
CX-24	1,2,3,6-tetrahydrobenzaldehyde
CX-25	3-pyridine carboxaldehyde
CX-26	2-chloro-6-fluoro benzaldehyde
CX-27	2-(4-chlorophenylthio)-benzaldehyde
CX-28	2-naphthaldehyde
CX-29	5-bromo-2-thiophene carboxaldehyde
CX-30	3-methyl thiophene-2-carboxaldehyde
CX-31	1-methyl pyrrole-2-carboxaldehyde
CX-32	cyclohexane carboxaldehyde
CX-33	2-thiophenecarboxaldehyde
CX-34	4-quinolinecarbocaldehyde
CX-35	9-ethylcarbazolecarboxaldehyde
CX-36	2,5-dimethylbenzaldehyde
CX-37	1-methyl-2-imidazole carboxaldehyde
CX-38	phenyl acetaldehyde
CX-39	1-(phenylsulfonyl)-2-pyrrole carboxaldehyde
CX-40	a,a,a-trifluoro-o-tolualdehyde
CX-41	2,4-dimethylbenzaldehyde
CX-42	2,4-difluorobenzaldehyde
CX-43	2-Fluoro-4-(trifluoromethyl)benzaldehyde
CX-44	3,5-difluorobenzaldehyde
CX-45	4-Fluoro-3-methylbenzaldehyde
CX-46	2-fluorobenzaldehyde

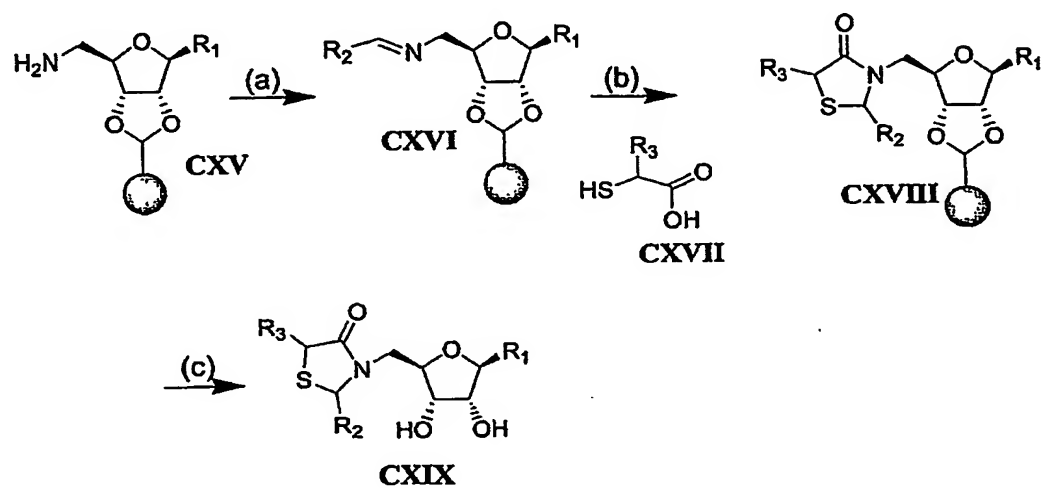
CX-47	2,5-difluorobenzaldehyde
CX-48	4-fluoro-3-(trifluoromethyl)benzaldehyde

Sugar Blocks – R³

Adenosine amine

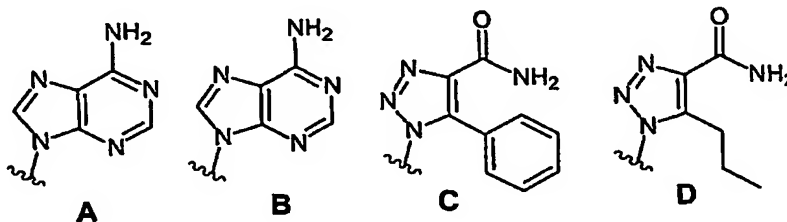
5 Phenyl triazole amine

Propyl triazole amine

Example 18: Synthesis of a library of thiazolidinones

5 **Conditions:** (a) R₂CHO, TMOF, THF; (b) mercapto acetic acid; (c) TFA/H₂O.

The substructures **A-D** listed below are substituents in the field **R1** in the libraries of compounds that follow.

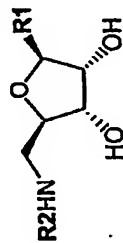


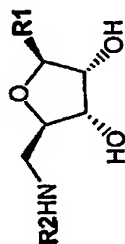
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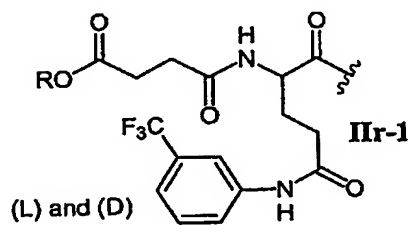
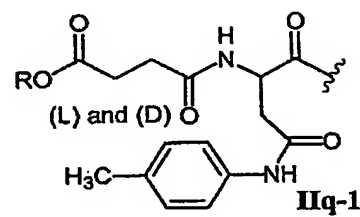
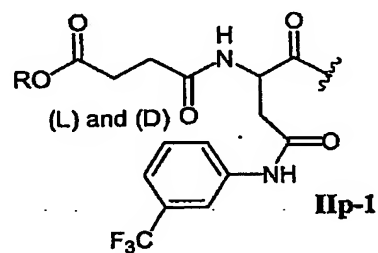
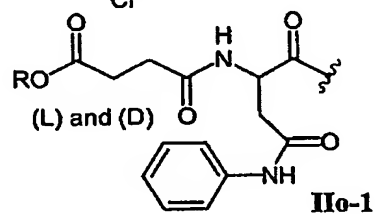
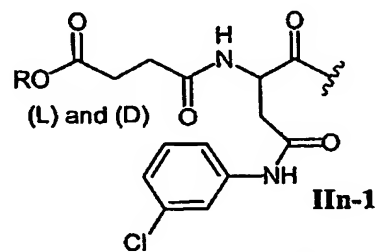
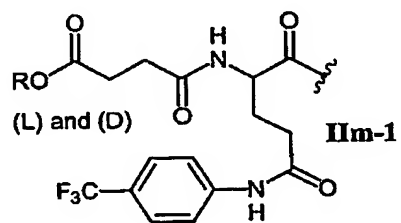
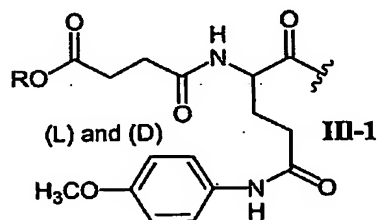
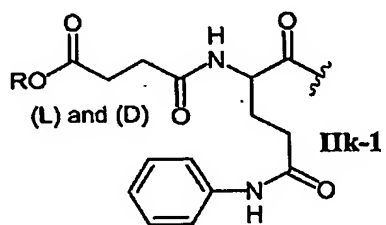
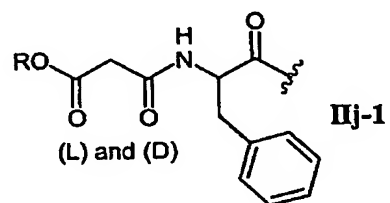
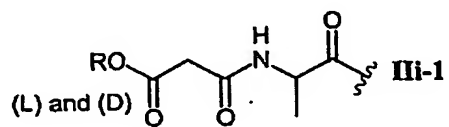
Others substituents referred to in the following libraries may be subsequently found in the text at the end of Exemplary Library 2 for substituents for libraries 1 and 2 and at the end of library 12 for substituents for the remaining libraries.

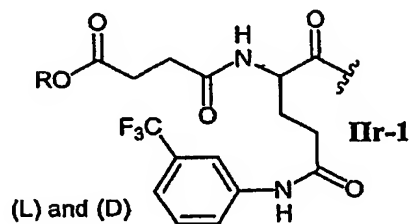
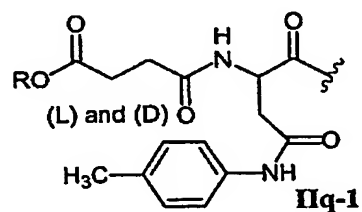
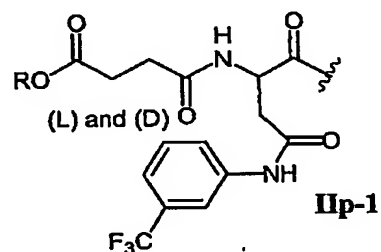
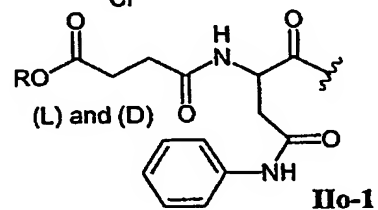
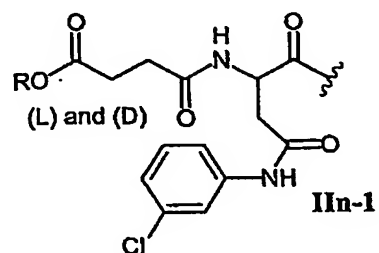
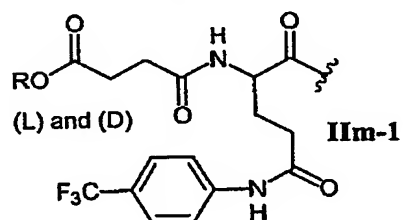
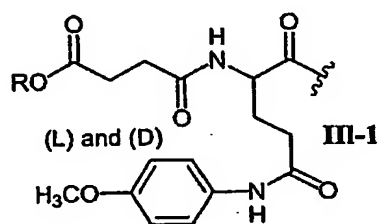
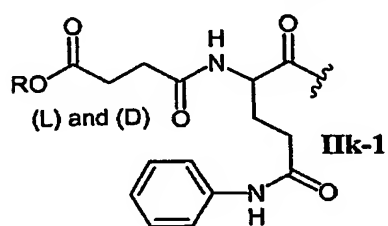
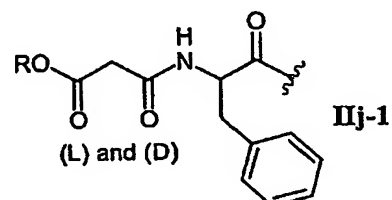
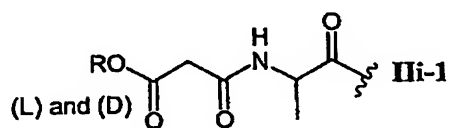
- 10 Active compounds referred to by the "+" symbol in the kinase assays **K1** to **K10** were determined under the assay conditions to have a residual enzyme activity of less than 70%. Inactive compounds in the respective assays were referred to by the symbol "-" and had a residual enzyme activity of greater than 70% as determined by the assay conditions. The kinase assay results **K1**
- 15 to **K10** are described as follows:

- K1** = Residual Activity of Enzyme ABL1
K2 = Residual Activity of Enzyme CDK2/CycA
K3 = Residual Activity of Enzyme EGF-R
 20 **K4** = Residual Activity of Enzyme FGF-R1
K5 = Residual Activity of Enzyme KIT
K6 = Residual Activity of Enzyme MET
K7 = Residual Activity of Enzyme PDGF-Ralpha
K8 = Residual Activity of Enzyme PKC-beta1
 25 **K9** = Residual Activity of Enzyme TIE2
K10 = Residual Activity of Enzyme VEGF-R2

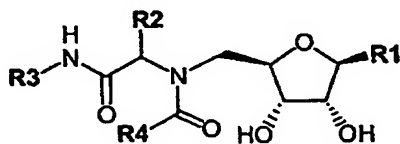
[illegible]

[illegible]





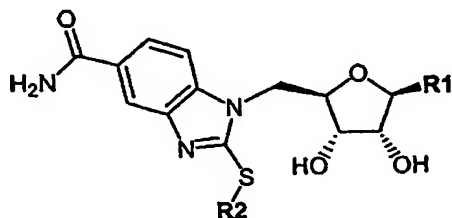
Exemplary Library 3:



5

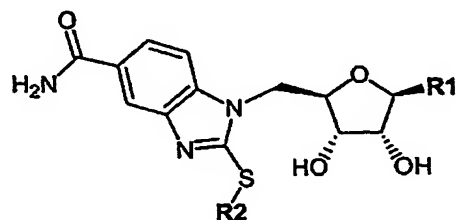
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Exemplary Library 4:

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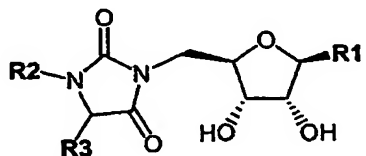
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Exemplary Library 5:

[illegible]

[illegible]

Exemplary Library 6:

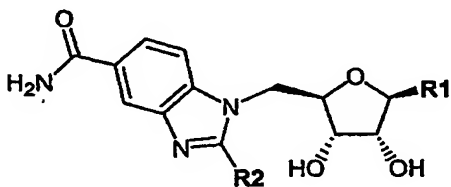


Comp.	R1	R2	R3	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10
197	A	$\pi 4$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
198	A	$\beta 1$	$\psi 1$	-	-	+	-	+	-	-	-	+	+
199	A	$\xi 1$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
200	A	$\epsilon 5$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
201	A	$\epsilon 2$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
202	A	$\sigma 1$	$\psi 1$	-	-	-	-	-	-	+	-	-	-
203	A	$\alpha 2$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
204	A	$\mu 1$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
205	A	$\tau 1$	$\psi 1$	-	+	+	+	+	+	-	+	-	+
206	A	$\tau 2$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
207	A	$\mu 2$	$\psi 1$	+	+	+	+	+	+	+	+	+	+
208	A	$\epsilon 7$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
209	A	$\mu 3$	$\psi 1$	-	+	+	-	+	-	-	-	+	+
210	A	$\gamma 2$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
211	A	$\gamma 5$	$\psi 1$	-	-	+	-	+	-	-	+	+	+
212	A	$\pi 4$	$\alpha 1$	+	+	+	+	+	+	+	+	+	+
213	A	$\beta 1$	$\alpha 1$	-	+	+	+	+	-	-	+	+	+
214	A	$\xi 1$	$\alpha 1$	+	+	+	+	+	+	+	+	+	+
215	A	$\epsilon 5$	$\alpha 1$	+	+	+	-	-	-	+	+	+	+
216	A	$\epsilon 2$	$\alpha 1$	-	+	+	-	-	-	-	-	+	+
217	A	$\sigma 1$	$\alpha 1$	-	-	-	-	+	-	-	+	+	-
218	A	$\alpha 2$	$\alpha 1$	-	+	+	+	+	-	-	+	+	+

219	A	$\mu 1$	$\alpha 1$	-	-	-	-	-	-	-	-	-	-
220	A	$\tau 1$	$\alpha 1$	+	+	+	+	+	+	+	+	+	+
221	A	$\tau 2$	$\alpha 1$	+	+	+	+	+	+	+	+	+	+
222	A	$\epsilon 7$	$\alpha 1$	-	+	+	+	+	-	-	+	+	+
223	A	$\mu 3$	$\alpha 1$	+	+	+	-	-	+	+	+	+	+
224	A	$\gamma 2$	$\alpha 1$	-	+	+	-	-	-	+	+	+	+
225	A	$\gamma 5$	$\alpha 1$	-	+	+	+	+	-	-	+	+	+
226	C	$\pi 4$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
227	C	$\beta 1$	$\psi 1$	-	-	+	-	+	-	-	+	+	+
228	C	$\xi 1$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
229	C	$\epsilon 5$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
230	C	$\mu 1$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
231	C	$\tau 1$	$\psi 1$	-	-	-	-	-	-	-	-	+	-
232	C	$\tau 2$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
233	C	$\mu 2$	$\psi 1$	+	+	+	+	+	+	+	+	+	+
234	C	$\epsilon 7$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
235	C	$\mu 3$	$\psi 1$	-	-	+	-	-	-	-	-	+	+
236	C	$\gamma 2$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
237	C	$\gamma 5$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
238	C	$\xi 1$	$\alpha 1$	-	-	+	+	+	-	-	+	+	+
239	C	$\epsilon 5$	$\alpha 1$	-	-	-	-	-	-	-	-	-	-
240	C	$\epsilon 2$	$\alpha 1$	-	-	+	-	+	-	-	-	+	-
241	C	$\sigma 1$	$\alpha 1$	-	-	+	-	+	-	-	-	+	-
242	C	$\alpha 2$	$\alpha 1$	-	-	-	-	+	-	-	-	-	-
243	C	$\mu 1$	$\alpha 1$	-	-	-	-	-	-	-	-	-	-
244	C	$\tau 1$	$\alpha 1$	-	-	-	-	+	-	-	-	+	+
245	C	$\tau 2$	$\alpha 1$	-	-	-	-	-	-	-	-	-	-
246	C	$\mu 2$	$\alpha 1$	+	+	+	+	+	+	+	+	+	+
247	C	$\epsilon 7$	$\alpha 1$	-	-	-	-	+	-	-	-	+	-

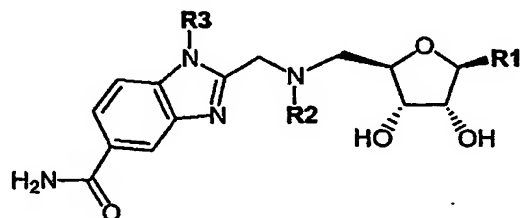
248	C	$\mu 3$	$\alpha 1$	-	-	+	-	+	-	-	+	+	-
249	C	$\gamma 2$	$\alpha 1$	-	-	-	-	-	-	-	-	-	-
250	C	$\gamma 5$	$\alpha 1$	-	-	-	-	+	-	-	-	-	-
251	D	$\pi 4$	$\alpha 1$	-	-	-	-	-	-	-	-	+	-
252	D	$\beta 1$	$\alpha 1$	-	-	-	-	+	-	-	-	+	-
253	D	$\epsilon 2$	$\psi 1$	-	-	-	-	-	-	-	-	-	-
254	D	$\sigma 1$	$\psi 1$	-	-	+	+	+	-	-	+	+	+

Exemplary Library 7:

[illegible]

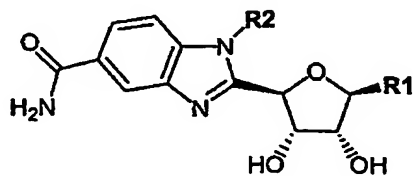
[illegible]

Exemplary Library 8:

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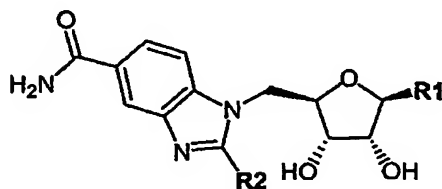
345	D	ψ_1	σ_3	-	+	+	+	+	-	-	+	+	+
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Exemplary Library 9

[illegible]

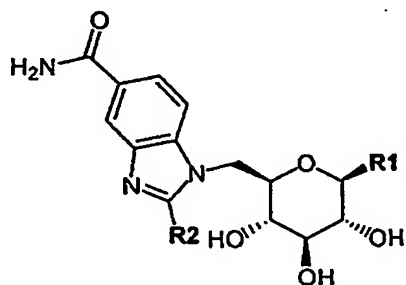
[illegible]

Exemplary Library 10:

[illegible]

[illegible]

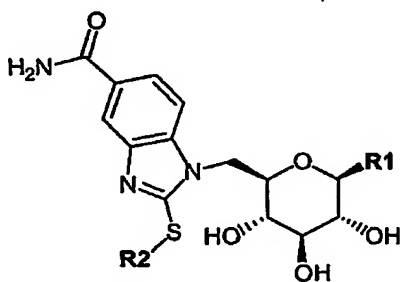
Exemplary Library 11:



Comp.	R1	R2	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10
457	D	θ1	-	-	-	-	-	-	-	-	-	-
458	D	β8	-	-	-	-	+	-	-	-	-	-
459	D	χ3	-	-	-	-	+	-	-	-	+	-
460	D	μ6	-	-	-	-	+	-	-	-	-	-
461	D	μ9	-	-	-	-	-	-	-	-	-	-

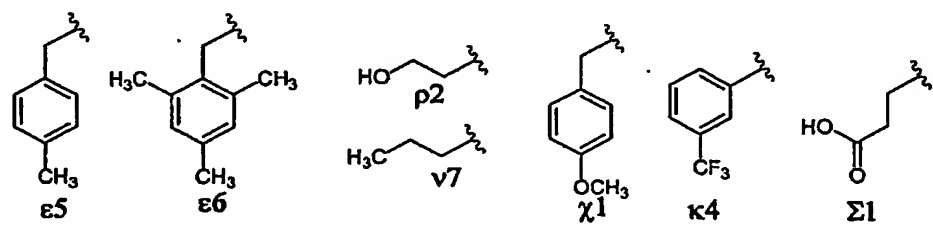
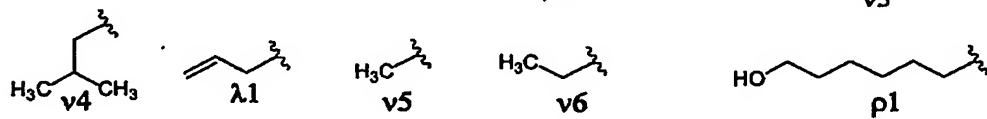
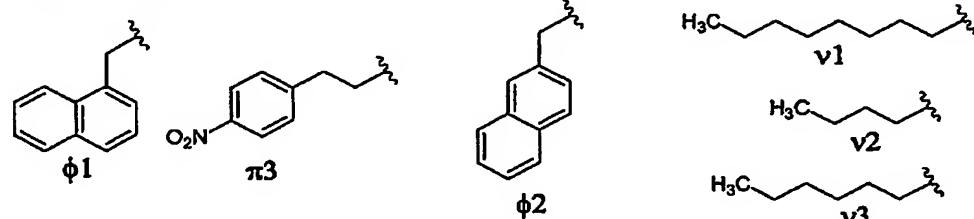
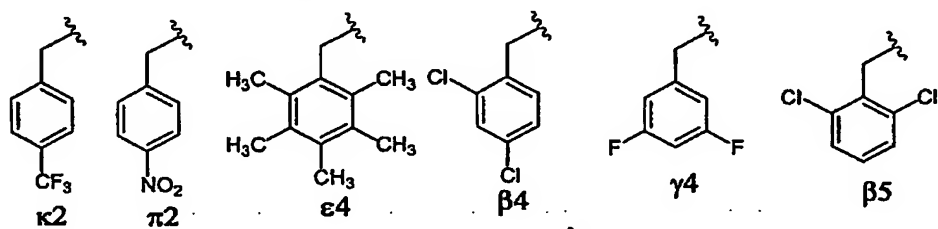
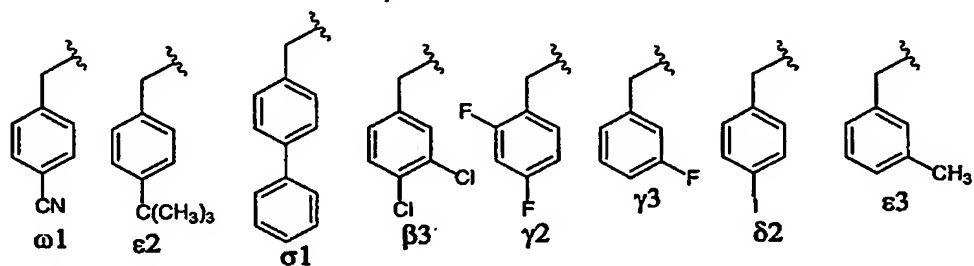
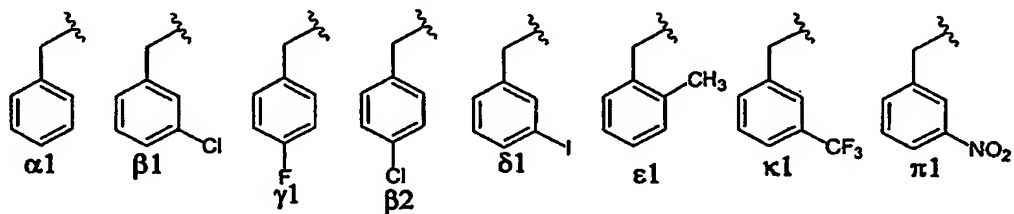
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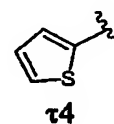
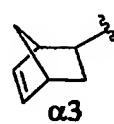
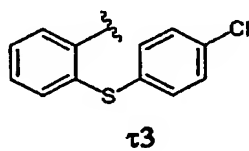
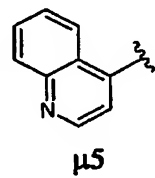
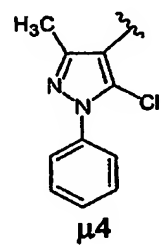
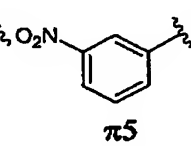
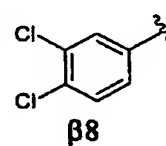
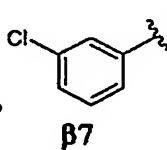
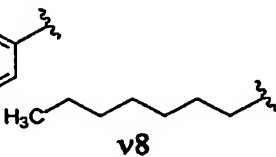
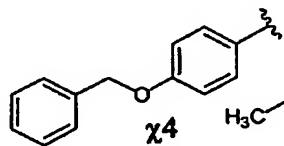
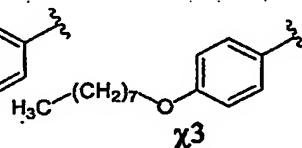
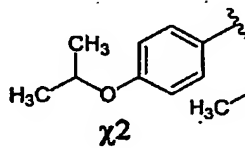
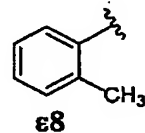
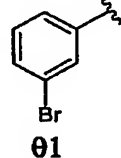
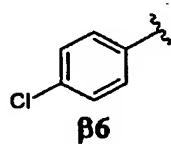
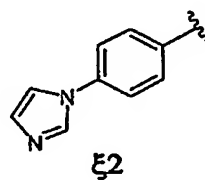
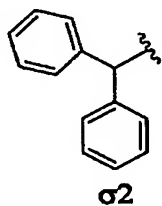
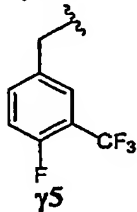
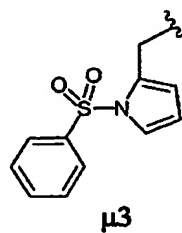
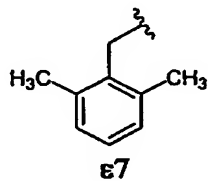
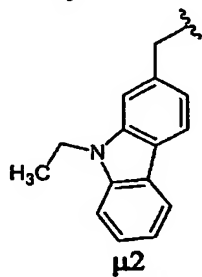
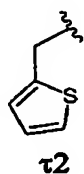
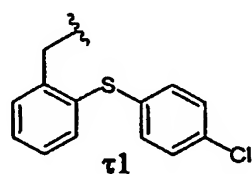
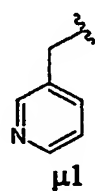
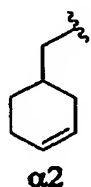
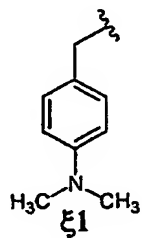
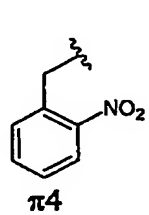
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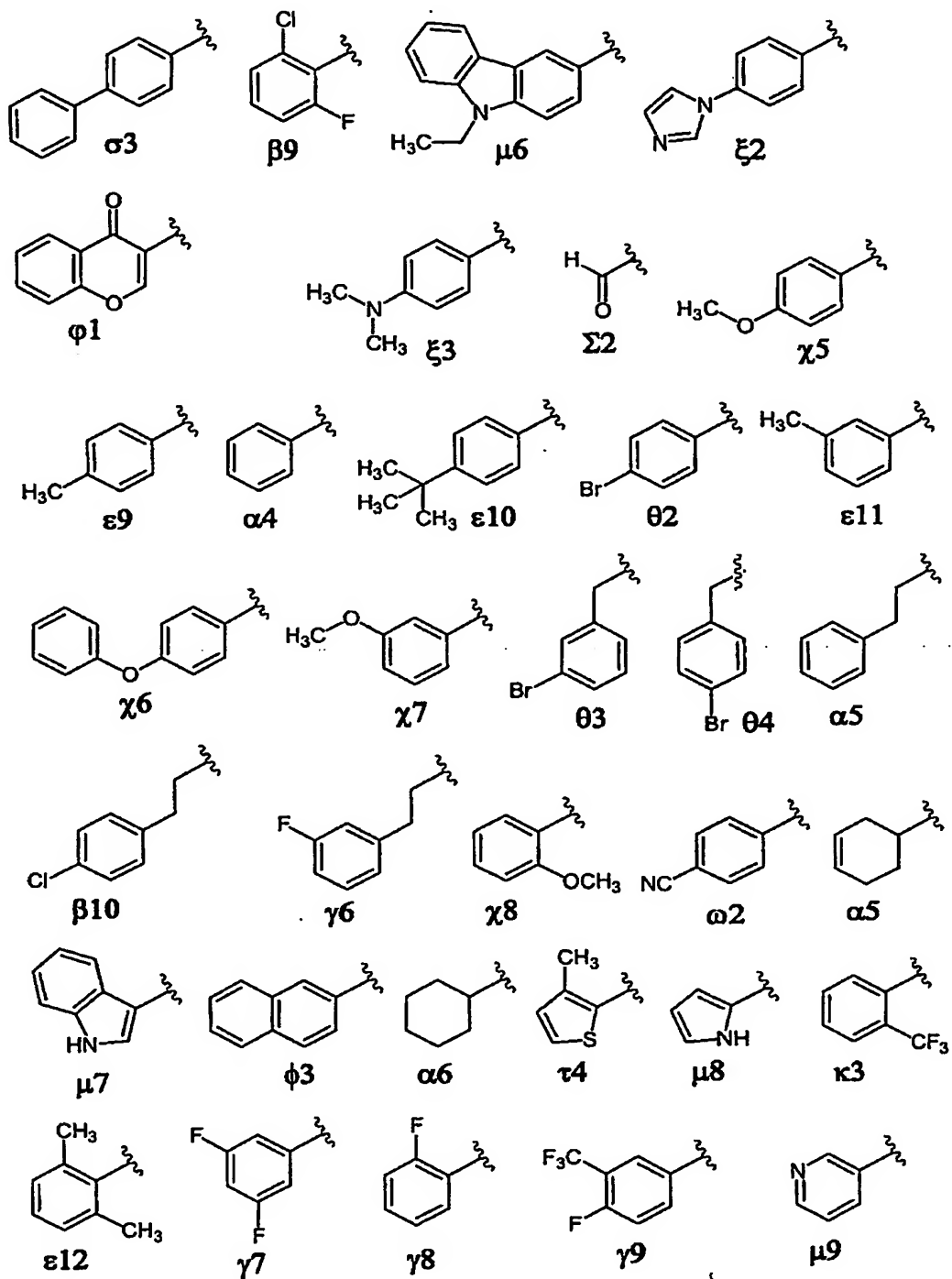


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Comp.	R1	R2	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10
461	D	ε2	-	-	-	-	+	-	-	-	-	-
463	D	σ1	-	-	-	-	+	-	-	-	-	-
464	D	δ2	-	-	-	-	+	-	-	-	-	-
465	D	β4	-	-	-	-	+	-	-	-	-	-
466	D	φ1	-	-	-	-	+	-	-	-	-	-







It should be appreciated that other changes and modifications can be made to the embodiments described without departing from the spirit and scope of the invention.

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Dated this 6th day of September 2002

Alchemia Pty Ltd

By their Patent Attorneys

Cullen&Co

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